EXHIBIT 18

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCT MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION ***This Document Relates to All Cases***	**Civil Action No. 3:16-md-2738-MAS-RLS** **MDL No. 2738**

THIRD AMENDED EXPERT REPORT OF JACK SIEMIATYCKI, MSc, PhD

Dated: May 27, 2024

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Jack Siemiatycki, MSc, PhD

EXPERT REPORT OF JACK SIEMIATYCKI MSc, PhD

on

TALCUM POWDER USE AND OVARIAN CANCER

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1. EXECUTIVE SUMMARY

I have reviewed the scientific evidence regarding causal links between use of talc-based powders by women and subsequent development of ovarian cancer.[1]

Evidence regarding this issue has accumulated since the 1970s and 1980s and continues to accumulate to this day. I have reviewed all of the relevant evidence from different scientific disciplines. I devoted particular attention to the key evidence from epidemiologic studies which have investigated the risk of ovarian cancer among women who had regularly used talc-based powders. There have been about 25-30 distinct informative epidemiologic studies, using different methodologies and conducted in different populations. There have also been several reviews and meta-analyses that attempted to summarize the evidence at the time of the respective review. While my focus was primarily on the epidemiological evidence documenting the associations between use of talc-based powders and ovarian cancers, there is also relevant experimental evidence concerning the nature of talc-based powders and the mechanisms by which talc-based powders can behave in the female body.

The scientific evidence, and most prominently the epidemiologic evidence, strongly supports the conclusion that there is an association between powdering and risk of ovarian cancer. While the individual studies do not all show statistically significant evidence of an association, nearly every study shows an estimate of the relative risk greater than 1.0, which is the measure used to quantify the nature of the association. When all the informative studies are combined in a meta-analysis, the best estimate of the relative risk is in the range of 1.25 to 1.35, indicating about a 30% excess risk of ovarian cancer among women who regularly used talc-based powders. This combined evidence is highly statistically significant. When available evidence was analyzed according to the cumulative amount of exposure to talc-based powders, it was seen that the relative risk increased as the amount of exposure increased. When available evidence was analyzed

[1] When I refer to talc or talcum powder products in this report, I am referring to commercially available talcum powder products and all constituent elements contained in those products.

according to histological types of ovarian cancer, there were some variations in risk within some studies, but these variations were not consistent from study to study; there is no convincing evidence that the risks are limited to one or more specific types of ovarian cancer.

Before concluding that an association between a putative risk factor and a disease is causal, it is necessary to consider potential sources of error and bias in the body of evidence. I have carefully considered a number of potential sources of error and bias, and conclude that these are unlikely to have created the artefactual illusion of an association between talcum powders and ovarian cancer.

Further, there are biologically plausible mechanisms to explain how powdering with talc-based powders can contribute to the development of ovarian cancer.

Based on the totality of the evidence, it is my opinion, to a reasonable degree of scientific certainty, that the perineal use of talcum powder products can cause ovarian cancer.

2. MY MANDATE AND STRUCTURE OF THIS REPORT

I have been retained to assess the epidemiologic evidence regarding the **general causation** between perineal (or genital) use of talcum powder products and the risk of ovarian cancer. I have specifically been asked to respond to the following questions: "Can application of talcum powder products in the perineal region cause ovarian cancer?"

This Report is designed to be informative to readers who are not familiar with me, with epidemiology and causal inference, or with the scientific evidence concerning use of talc-based powdering and risk of ovarian cancer. There is a section outlining my expertise and experience, a section outlining the essential features of epidemiology that are needed to understand the material that is germane to the topic of the mandate, a series of sections that outline the evidence regarding talc and cancer, including a meta-analysis that I have carried out, some sections devoted to the inferences that the evidence supports, and finally my own conclusion about the question posed in the mandate.

3. MY CREDENTIALS, EXPERTISE AND EXPERIENCE

I am a tenured Professor of epidemiology at the University of Montreal and an Adjunct Professor of epidemiology at McGill University in Montreal. I have received prestigious national research awards in Canada, such as the National Health Scientist Salary Award, Medical Research Council of Canada Distinguished Scientist Award, the Guzzo-Cancer Research Society Chair in Environment and Cancer and the Canada Research Chair in Environment and Cancer. I am an elected Fellow of the Canadian Academy of Health Sciences. I was awarded a lifetime achievement award by the Canadian Society for Epidemiology and Biostatistics in 2011, the premier professional organisation in our discipline.

Trained in statistics and in epidemiology, I have devoted most of my research career to investigating links between environmental, occupational and lifestyle factors and various types of cancer. My research has been both substantive – namely, looking at particular factors and their possible relationship to particular cancers - and methodological – namely, exploring how to evaluate and enhance the validity of epidemiologic research through various prisms: study design, data collection methods and statistical analysis. Of my approximately 340 research publications, about one quarter would be considered to have a methodological focus.

I have held various leadership positions, including the elected presidency of the Canadian Society for Epidemiology and Biostatistics, and elected membership on the Board of the American College of Epidemiology. I have been invited to serve on over 160 Boards, Scientific Councils and Expert Panels for a host of governments, universities or research agencies. Examples include: Board of Directors of the Canadian National Cancer Institute, member of expert panel tasked with recommending priorities for action under the Canadian Environmental Protection Act, member of external peer review panel of the Epidemiology branch of the US National Cancer Institute (NCI), member of two different expert advisory bodies to research projects at the US National Cancer Institute, consultant to the panel on cancer research priorities that reported to President Bill Clinton, member of external peer review panel for the Helmholtz German national medical research agency, Chair of the Scientific Council of the largest prospective study of causes of cancer being conducted in France, and others.

I have been associate editor of the American Journal of Epidemiology and the International Journal of Environmental Health. In addition, I have served as reviewer for about 20 journals. I have served as a chair and as a member of grant review panels for major Canadian scientific funding agencies.

My research programme has been well funded by Canadian funding agencies for over 40 years. I have conducted research and published on the carcinogenicity of a large number of agents in the occupational environment (e.g. asbestos, silica, welding fumes, talcum powder) and in the general environment (e.g. smoke from wood stoves, urban air pollution) and lifestyle factors (e.g. smoking, alcohol, use of cell phones).

I have taught and supervised epidemiology students and many of my former trainees are now faculty members in universities around the world.

I have had a long association with the International Agency for Research on Cancer (IARC). IARC is the premier institution in the world for cancer epidemiology and for environment and cancer research. It has several mandates, including the organization and compilation of standardized high quality data on cancer incidence around the world, the conduct of original research, and the evaluation of the carcinogenicity of different agents with which humans come into contact. Since the inception of the program to systematically evaluate possible carcinogenicity of chemical agents in 1971 (widely known as the IARC Monograph program), there have been about 134 meetings held and approximately 1200 agents have been evaluated. Research results from my team have been cited as part of the information base on over 70 of the 1200 agents that have been evaluated, making my team one of the most, if not the most, cited epidemiology teams in the history of the IARC Monograph program.

My association with IARC began when I did a post-doctoral fellowship there in 1977-79. Over the intervening years I have collaborated with scientists at IARC on various research projects. I was a member of the 18-member Scientific Council of IARC from 2006 to 2010 including two years as elected Chairman of the Council. The Scientific Council oversees all of the scientific activities at IARC; its members are named by the member states of IARC. I have been invited to sit on IARC Monograph international expert panels for 5 of the 70 panels convened in the past 25 years. One of the IARC Monograph panels of which I was a

member was tasked with evaluating: "Carbon black, titanium dioxide and non-asbestiform talc." Out of the 16 invited experts who participated in the meeting as members of the Working Group, I was selected to chair the meeting.

Subsequent to the IARC meeting and the report of the meeting, a small subgroup of members of the IARC Working Group, of which I was a member, conducted and published a meta-analysis of the results of the studies that had been available to the IARC Working Group. (Langseth, 2008)

In addition to the above, I have participated as a co-investigator and methodological mentor in a study of ovarian cancer that a young colleague of mine at the University of Montreal, undertook a decade ago. That was a case-control study conducted in Montreal and it was intended to investigate a host of genetic, environmental and lifestyle factors in the etiology of ovarian cancer. Some results have already been published.(Leung 2019; Grundy 2020; Leung 2023) While information on use of talc was collected, that part of the dataset has not yet been analysed and published.

I am well qualified to review the epidemiologic evidence on talc use and ovarian cancer. I have participated in two published reviews of the issue. The methodologic expertise and analytical skills required to critically review and evaluate such evidence is generic to the vast area of environmental epidemiology of cancer. I am routinely asked by journals and grant agencies to provide expert opinions on topics for which I have not produced original data collection studies, but that are within the purview of my methodological expertise. While I do not claim expertise in various adjoining domains that inform this issue, including physiology, pathology, clinical oncology, experimental toxicology, geology and mineral chemistry, I have the expertise and skill to assimilate information that is provided by experts in these areas.

I have previously served as an expert witness for plaintiffs in the U.S. talc litigation in Los Angeles in 2017. (Eva Echeverria, BC628228, Johnson and Johnson Talcum Powder Cases, CA JCCP No. 4872), and I testified that talcum powder products can cause ovarian cancer.

I have previously been qualified as an expert witness by Quebec courts on behalf of both plaintiffs and defendants. Specifically, I was an expert witness for the defence, the Canadian government, in a class action lawsuit brought on behalf of residents of a town in

Quebec adjoining a Canadian military base where there had allegedly been a spill of trichloroethylene that seeped into the water table of the town. The residents claimed that the contamination had caused cases of cancer. (Province of Quebec Superior Court file 200-06-000038-037).

I served as an expert witness on behalf of plaintiffs and testified in 2014 in a class action on behalf of Quebec residents who contracted cancer and had been smokers, claiming that the tobacco companies were responsible for their diseases. (Province of Quebec Superior Court file 500-06-000076-980).

My curriculum vitae is attached as **Exhibit "A".** In my work as an expert for legal cases, my time is billed at the rate of $600 per hour for research, report preparation, communications with counsel, participation in depositions, and testimony in court.

I reserve the right to amend my report upon review of further scientific information. I also reserve the right to review and comment on the expert reports submitted by the defendants.

4. OVERVIEW OF MY METHODOLOGY

The basis of my opinions derive from my education, training, experience, research and what is accepted within the community of leading scientists practicing in the field of epidemiology. My opinions are based on my review of the relevant materials, published in the scientific literature as well as publicly available documents, relevant depositions, reports and testimony in the talcum powder product litigation. To reach my conclusions, I have employed the same scientific methodology and rigor that I use in my research, in my publications and in the consulting and advising that I carry out on behalf of governments, public health agencies and research institutes. This includes a review of the relevant published literature, expert judgment to assess the quality and meaning of the various studies that were reviewed, and syntheses of the available evidence and any other pertinent medical and scientific evidence of which I am aware.

The methods I used to derive and present my opinions are those used in general in the assessment of causal relations in medicine and public health, and more specifically in epidemiology. The methods are based on the experience and insight I have accumulated

over 40 years of research, consulting, reviewing and student supervision, from discussions and interactions with leading epidemiologists, service on multiple IARC panels, and from reading evolving ideas in the scientific literature, including such seminal works as Bradford Hill's (Hill 1965) writings on assessing causality.

5. THE SCIENCE OF EPIDEMIOLOGY

This section is designed to provide a non-specialist reader with information and definitions about epidemiology and biostatistics that are needed to understand the basis of my evaluation of the relationship between talcum powder products and ovarian cancer. It is intended for readers who are not familiar with the terminology and methods of epidemiology. In this section I will not tie the concepts and definitions of epidemiology to the talc-ovarian cancer issue; that part will be left for later. Thus, the reader already familiar with epidemiology can skip over this section to go straight to the evidence that I will lay out.

Epidemiology is the science of occurrence of diseases in human populations. It is concerned with the patterns of disease occurrence and with identifying the factors that influence disease occurrence. These two sets of concerns are sometimes referred to respectively as descriptive epidemiology and analytic epidemiology. The first addresses such issues as the incidence of the disease in different geographic areas, in different time periods, or at different ages and sexes. The second addresses more focused questions on the specific environmental and/or lifestyle and/or genetic factors that might influence the incidence of disease.

Epidemiology initially grew out of the study of epidemics. Such epidemics were often of a microbial origin (e.g. viruses, bacteria, parasites). But increasingly in the 19th and especially in the 20th century, it became clear that the etiology (i.e. causation) of chronic diseases such as cancer could also be elucidated by studying their patterns of occurrence.

Epidemiology is characterized by its mainly observational and non-experimental approaches. It is a discipline that is not primarily based in the laboratory; rather it is based in society. That is the source of its strength, and its weakness. Because it deals with people in the reality of their lives, it is the most pertinent approach to understanding the links

between people's lifestyles and environments and their health and disease. However, because it is based in society, it by necessity confronts the extreme complexity of human lifestyles, environments and diseases. And because we cannot experiment with people's lives, we cannot control the conditions in which people are exposed. The methods of epidemiologic research are complex and differ from study to study. Statistical methods play an important role in trying to tease out the role of different variables and in determining whether the observed results may be attributable to chance, to bias or to real effects of putative risk factors. It is usually necessary to assemble evidence from several data-collection studies on a given topic before being able to draw inferences about causality.

5.1 Some basic measures and notions used in epidemiology

In this section I will review a number of concepts that need to be understood in order to properly understand a review of the evidence regarding talc powder and ovarian cancer.

Prevalence of disease. The prevalence of a disease refers to the proportion of a population who are living with the disease at any given point in time.

Incidence of disease. The incidence of a disease refers to the proportion of a population who are newly diagnosed with the disease during a certain period of time. The bridge between incidence rate and prevalence rate is the average duration of the disease, or how long people live with it before they are cured or pass away. In fact, while incidence and prevalence are foundational concepts in epidemiology, it is only incidence that figures prominently in the evaluation of carcinogenicity of talc.

Risk of disease. The risk of disease is a term that can refer to incidence or prevalence. The meaning should be clear from the context in which it is used. For studies of cancer, it almost always refers to incidence of disease. This is the way I will use the term in this report.

"Cause" of disease. A cause of a disease is any agent or characteristic (environmental, lifestyle or genetic) that increases the probability of getting the disease or it may simply advance or hasten the onset of the disease. It may act alone or in concert with other factors over a lifetime to cause the disease. It may act immediately (e.g., cyanide as a cause of poisoning; lack of seat belt use as a cause of car accident mortality) or it may take many

years for the effect to become manifest (e.g., lack of physical activity as a cause of obesity). There may be many different causes for the same disease. (See explanation of Multifactorial Etiology below.)

Risk factor. As defined in the Dictionary of Epidemiology (Last 2001), a risk factor is an aspect of personal behaviour or life-style, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is considered to be associated with a health-related condition. The term *risk factor* is used rather loosely and depending on the context it can refer to a factor that directly causes a disease or a factor that is a strong marker for the proximal cause of the disease. As it is often used, I will mainly use the term "risk factor" as a synonym for the noun "cause" of the disease. (e.g. "Smoking is a risk factor for lung cancer.")

Association. As defined in the Dictionary of Epidemiology (Last 2001), association refers to the degree of statistical dependence between two or more events or variables. Events are said to be associated when they occur more frequently together than one would expect by chance. Association does not necessarily imply a causal relationship.

Risk among unexposed (R_u) refers to the risk of disease among persons who are not (or were not) exposed to the agent under investigation. In the context of an investigation of the association between use of talc powder and ovarian cancer, it would refer to the risk of getting ovarian cancer among women who *have never* used talc in the perineal region.

Risk among exposed (R_e) refers to the risk of disease among persons who are (or were) exposed to the agent under investigation. In this context, it would refer to the risk of getting ovarian cancer among women who *have* used talc in the perineal region.

Relative Risk: RR = R_e/R_u = Risk among exposed/Risk among unexposed

When RR > 1.0, it indicates that exposure to the agent increases the risk of developing the disease. When RR < 1.0, it indicates that exposure to the agent prevents the disease.

When RR = 1.0, it indicates that the exposure to the agent has no bearing on the risk of getting the disease.

95% Confidence interval (95% CI). This refers to the precision of an estimate of a parameter. When we estimate the 95% CI for the RR, we are saying that we are 95%

certain that the true parameter underlying the study is within these limits. (The mathematically true interpretation is more subtle, but this lay version is quite adequate.)

Statistical significance of an association: Statistical significance is a measure of the departure of a set of data from some null hypothesis. Most commonly in epidemiology, the null hypothesis would state that there is no association between a factor and a disease. The null hypothesis can be operationalized in different ways, such as that the RR = 1.0, or that there is no trend between the degree of exposure and the RR. Once a study is conducted, the results can be compared with the expected results based on the null hypothesis, and the discrepancy from the null hypothesis is measurable with probabilities. This is done either by computing a p-value or a confidence interval. If the p-value is very small or the confidence interval does not include the null value, then we say that an observed association between the putative risk factor and the disease is unlikely to be due to chance alone.

It is important to note that while statistical significance is a tool for assessing whether an observed association is attributable to chance alone, it is not a very effective tool for establishing the absence of an association. That is, the absence of statistical significance is not tantamount to proof of the absence of an association. (Rothman 2008; Amrhein 2019) The absence of statistical significance can be due to the true absence of an association, but it can also be due to the study not having sufficient statistical power or to bias or confounding in the research methods. Furthermore, it should be noted that the conventional dichotomization of results as "statistically significant" or not, based on a particular cut-point on the p-value scale (e.g., p = 0.05), is a gross simplification. The compatibility of the data with the null hypothesis of no association is in truth on a continuous scale and the dichotomization is arbitrary and potentially misleading, especially when the observed p-value is close to the arbitrary cut-point.

In practice, epidemiologists have been moving away from using and reporting p-values and statistical significance, as it has become clear that the main contribution of an individual study is to provide an estimate of the relative risk and its range of plausible values, embodied in a confidence interval. (Amrhein 2019; Wasserstein 2016)

Cohort studies and case-control studies: Epidemiologic research projects can take many different forms. The two most common types of analytic epidemiologic studies are cohort studies and case-control studies. (Rothman, Greenland, & Lash 2008)

In a cohort study, it is typical to enrol a large number of subjects, determine which ones are or have been exposed to the factor of interest (e.g., talc) and follow them for some period of time to evaluate whether those who were exposed subsequently experienced different disease rates from those who were not exposed.

In a case-control study, by contrast, we start with people who have the disease under study (e.g. ovarian cancer) and a set of controls who do not have the disease, and we collect data to determine whether the cases and the controls had different histories of exposure to the factor under study (e.g. talc).

It may be said that a cohort study proceeds from the cause to the effect, whereas a case-control study starts from the effect and backtracks to the cause. There are many variants on these basic designs.

It is sometimes claimed that a prospective cohort design produces more valid and reliable RR estimates than a case-control study. But this is incorrect as a generalization. The validity and reliability of the studies are not determined by the overall architecture of the study, but rather by the specifics of the study, including how the study subjects were assembled, the nature of the variables under study (exposure, disease, confounders), exactly how the information was collected, the statistical power, and so on. There may be many reasons why a particular case-control study is more valid than a particular cohort study.

Relative Risk (RR) and Odds Ratio (OR). The cohort study design leads naturally to the estimation of risk of disease among exposed, and risk of disease among unexposed, and then to the ratio of those two, which is the RR. In case-control studies, because of the way the study samples are selected, it is impossible to estimate the risk of disease or the ratio of the two risks, R_e/R_u. However, under certain conditions which are well met in studies of cancer, it is possible to estimate an approximation of the RR. This is called the odds ratio, referred to as OR. In the rest of this report, I will consider evidence obtained from

both cohort studies and case-control studies, and I will refer to the findings of these studies as RRs, even if technically speaking, the results from case-control studies are ORs.

Bias, confounding, effect modification. The aim in an epidemiologic investigation of a putative risk factor is to derive an accurate estimate of the RR between exposure to the agent and the disease at issue. Because the investigator does not control the conditions in which people live and are exposed to different agents and their willingness to participate in research, there are many potential sources of distortion in epidemiologic research. While there are many sources of distortion, they can be bundled into a few large families of sources of distortion. Different epidemiology textbooks bundle the sources of distortion in different ways; the choice of how to bundle them does not affect our understanding of the issues. Following is my preferred schema for organizing these issues.

Bias refers to a systematic distortion in study findings, resulting from the way the study was designed or the way the data are collected. Specific examples of types of bias will be discussed below as they pertain to talc and ovarian cancer.

Confounding is sometimes considered to be a type of bias, and sometimes it is considered a type of distortion on its own. This is merely a semantic distinction. Confounding refers to the situation where the association under study between factor F and disease D is distorted because there is a third factor X which happens to be correlated with F and which is a cause of disease D. For instance, if we want to study the association between occupational exposure to talc in mines (factor F) and lung cancer (disease D), we need to be mindful of whether cigarette smoking (factor X) is more common in talc miners than in the rest of the population. Confounding differs from other types of bias in that it depends on relationships among different variables in the population, rather than characteristics of the study design and data collection.

Effect modification refers to the phenomenon whereby a given factor has a different effect in one sub-population than in another. If we study the association between that factor and the disease in the entire population without distinguishing the two sub-populations, we might end up with an estimate of the association that does not convey accurately the association in either sub-population. For instance, if it were the case that a certain genetic characteristic G increases the risk of pre-menopausal ovarian cancer but

has no impact on post-menopausal ovarian cancer, then a study of the association between G and ovarian cancer that does not stratify the data by menopausal status, would find an RR result somewhere between the null value among post-menopausal women and the RR value among pre-menopausal women. Depending on the proportions of pre- and post-menopausal women in the sample, the overall RR might be so close to the null, that we might erroneously conclude that there is no association at all. In this example, it might actually be quite simple to detect the effect modification, since age is always recorded and menopausal status is usually recorded and investigators are sensitized to the possible effect modification of female cancers by hormonal status. Other potential effect modifiers may not be so easily available and they might not be on the radar screens of investigators. Effect modification can in some unusual circumstances completely wipe out a true causal association (as when the agent causes cancer in some people but prevents cancer in others!). But generally, if there is a causal effect of the agent in one stratum of the population and no association in another stratum, and if we fail to stratify the population according to the effect modifier, it will have the effect of producing an overall RR that is lower than it truly is in the sensitive stratum and higher than it truly is in the insensitive stratum.

Effect modification is closely related to and sometimes synonymous with interaction or synergism.

Publication bias refers to the tendency for some evidence never to "see the light of day". Namely, when results are "negative" or "null", it may be that investigators never bother to submit them for publication, or alternatively that editors refuse to publish them. This happens, most likely, when the hypothesis under study is not particularly topical or controversial, and when the study is small.

In this section I have briefly outlined some potential sources of distortion of a typical epidemiologic study. I have done this in a high-level generic way. Below, after presenting results of my review of pertinent literature on powders and ovarian cancer I will return to commenting on the possible impact of such distortions in this body of literature.

Exposure variable and exposure metric

An ***exposure variable*** can be anything that can influence the occurrence or outcome of disease. The term is used for such disparate entities as external components of what we eat, drink, breathe, hear or see and microbiological organisms, chemicals or forms of radiation.

Depending on the nature of the variable, information on an exposure variable can often be ascertained from epidemiologic study participants by questioning them. This is the case for variables like cigarette smoking or use of talc powders. For some variables, like exposure to a virus or to specific air pollutants or occupational chemicals, it is usually necessary to invoke more intensive data collection methods to ascertain exposure.

An ***exposure metric*** signifies a way of defining a variable for statistical analysis. The simplest metric is a binary variable: exposed or unexposed. For most exposure variables, like exposure to talc powder, there can be a very wide range of degree of exposure. And it is pertinent to create more nuanced exposure metrics that take into account the degree of exposure that different people have experienced, metrics such as duration of exposure, intensity or frequency of exposure and even cumulative measures of exposure over long periods of time.

Measurement error. Whenever we are measuring a variable in an epidemiologic study, be it smoking, or weight, or socio-economic status, or blood pressure, or any other variable, it is virtually inevitable that there will be some degree of error in the measurement. There are ways of collecting data that make them more or less likely to involve error, but it is almost impossible to ensure that variables are measured with perfect validity and precision. Even such a variable as the diagnosis of ovarian cancer is subject to differences of opinion among pathologists and oncologists and the presence or absence and the histologic type of tumour is not a guaranteed 100% perfect diagnosis. The ascertainment of the lifetime history of talc exposure by means of an interview with a woman in middle age or later in life is certainly susceptible to the caprices of memory and the way the questions are formulated may influence the validity of respondents' reports of lifetime exposure patterns. It is likely that habits that were performed regularly and recently are more reliably recalled than activities that were sporadic or that only occurred

many decades earlier. Similar issues arise for all other variables collected in such studies. We refer to measurement error as random (or non-differential) if the degree of measurement error does not differ between cases and controls in case-control studies or between exposed and unexposed in cohort studies. As a general rule, it can be asserted that random (or non-differential) measurement error has a predictable distorting effect on the RR. Namely, while there are some rather obscure exceptions, non-differential measurement error tends to attenuate the RR towards the null value of 1.0, and the more measurement error, the greater the attenuation. A simple explanation is that the presence of measurement error in assigning exposed vs unexposed status leads to dilution of both the exposed group and the unexposed group. That is, the ostensible exposed group (i.e., those people who will be labelled as exposed based on the study data collection) will contain some who are truly unexposed and the ostensible unexposed group will contain some who are truly exposed. If there really is a difference in risk between the true exposed group and the true unexposed group, this difference will be watered down by the inadvertent inclusion in each group of those who are really in the opposite group. An illustrative analogy is the cross-contamination of two cans of paint. Suppose we have a can of pure white paint and a can of pure red paint. Suppose we have a way of quantifying the difference in colour tone between the two paints. Then suppose we take some spoonfuls from the red can and pour them into the white can, and likewise take a few spoonfuls of the white paint and pour them into the red can. Now the colour contrast between the two cans has been attenuated. The colour contrast in this example is like the relative risk in an epidemiological study which has been attenuated because the exposed and unexposed groups have been cross-contaminated.

Dose-response. It is important not only to assess whether there is an association between a variable and a disease when the variable is defined in a binary (exposed vs unexposed) way, but also when the variable is defined in a quantitative or semi-quantitative way. When we analyze the risk as a function of the degree or duration or intensity of exposure, we refer to this as a dose-response (or exposure-response) analysis. The example of smoking and lung cancer is instructive about the value of different metrics, though it cannot be assumed that all risk factors act the same way. Studies using the binary metric for smoking (smoker/non-smoker) have been very consistent and persuasive in

demonstrating an association between smoking and lung cancer. Further, when data are collected and analyzed regarding the degree of smoking, it becomes clear that there is a monotonic dose-response relationship. That is, the more smoking, the higher the risk. And the quantitative metric that manifests the strongest association with lung cancer is the cumulative amount smoked over the lifetime. This is perfectly logical. Since the cumulative exposure metric embodies information on duration and on intensity, it can hardly be less predictive of risk than either of the dimensions alone.

However, we cannot assume that there is a universal form of a dose-response relationship for every true causal relationship. Most commonly, in toxicology and epidemiology, the relationship between exposure and risk is monotonic; that is, as one increases, so does the other. There are many possible forms of monotonic relationships; this includes linear relationships (i.e., where a straight line on a graph describes the relationship) or exponential or many other curvilinear forms. It is also possible that there may be a threshold effect (the risk only becomes apparent after a certain level of effective exposure) or some other non-standard relationship.

Both the qualitative metrics (ever/never) and quantitative metrics (a lot of use compared with a little use) are valid and useful metrics.

Sample size refers to the number of participants in the study. As a generalization, large studies produce more statistically stable and precise estimates than small studies. In fact, the stability of estimates or precision of estimates is not a simple function of the number of participants, or subjects, in a study. The precision of estimates depends, among other things, on the type of epidemiologic design.

In a case-control study, the main determinants of precision are the numbers of cases and controls and the prevalence of exposure in the two groups. In a cohort study, the main determinants are the numbers of participants, prevalence of exposure, and the incidence of the disease of interest over the period of follow-up in the exposed and unexposed groups.

There is sometimes confusion about the notion of sample size when we compare cohort studies with case-control studies. The operational aspect of an epidemiologic study of cancer that most influences the precision of an estimate of RR is not the total number of

participants; rather, it is the smaller number between the number of exposed cases of disease and the number of unexposed cases. In a typical prospective cohort study, one might need to enrol 100,000 participants in order to end up with a certain number of cases (say, 500 cases) of the disease of interest (e.g. ovarian cancer). In a case-control design we might only need to enrol around 500 cases and 1500 controls to achieve the same statistical power as would be achieved by a cohort study of 100,000. The formal justification for this assertion is quite mathematical, and has to do with the fact that a sample of a population can give very accurate estimates of the characteristics of an entire population. Thus, the simple comparison of 100,000 participants in a cohort study and 2,000 participants in a case-control study is in no way a valid marker for the relative statistical power of the two hypothetical studies. It is definitely not appropriate to merely compare the numbers of participants as an indicator of study validity.

While precision is based on multiple factors and while different factors are considered in case-control and cohort studies, there is a parameter which embodies the different factors quite well, and which is common to both case-control and cohort studies, namely, the number of exposed cases. For this reason, in laying out the various study results below, in addition to the relative risk estimates and their confidence intervals, I will show the numbers of exposed cases.

While it may affect the precision of estimates of RR, the size of the study does not in itself systematically affect the estimates of RR. That is, it is not the case that small studies produce systematically exaggerated RR estimates or systematically low RR estimates. However, small studies can produce more wildly divergent RR estimates than large ones, in either direction, towards the null or away from the null.

Meta-analysis and pooled analysis. There are two distinct ways that evidence from multiple studies can be combined to derive a new overall statistical summary or synthesis of those studies, a meta-analysis and a pooled analysis. A meta-analysis uses the published results from each study and averages those results using some optimal weighting procedures. In order to implement a meta-analysis, it is necessary to find all relevant studies on a topic that have published results in a fairly standardized way. The statistical algorithms typically used to average the results from different studies also

provide statistics that evaluate the extent to which the results from the different studies are heterogeneous. The interpretation of such heterogeneity statistics is not straightforward. If the results from different studies are homogeneous, they add to the confidence in the meta-estimate. If the results are heterogeneous, they may indicate that the association is really different in different populations, or that there are some methodological characteristics of the different studies that have influenced the results in different ways. Unless a significant methodological flaw can be identified that has caused the heterogeneity, the best overall estimate remains the meta-estimate.

A pooled analysis is one in which the investigator gets access not only to the published results from different studies, but rather to the individual data of every person in each study. The latter is harder to achieve because it requires a great deal of input, collaboration and participation of the investigators of each of the original component studies. By contrast, a meta-analysis is much easier to organize as it requires the investigator to only assemble the publications of each study. Because a pooled analysis allows for standardization in the definition of variables and statistical models, it can be a more powerful means of summarizing data than the original studies themselves.

Multifactorial etiology of disease. Chronic diseases such as cancer are multifactorial in two distinct ways. On the one hand, each case of disease results from the unfortunate conjuncture of a combination of factors (for example, genetic predisposition, diet, environmental pollutant, occupational exposure, medical intervention, viral infection, lifestyle habits, etc.) which combine over a lifetime to initiate and promote development of the disease. In this sense, each of the factors that are part of the combination for that person was a necessary contributor to the disease process, although it was not sufficient on its own to provoke the disease. Despite the fact that none of the factors were sufficient to produce the disease on their own, each of the contributory factors may be considered to be a cause of the disease. The disease would not have arisen if any of the contributory factors had been absent. This is one meaning of the multifactorial etiology of disease.

The second meaning is that the combination of factors that induce cancer in one person may not be the same as the combination that induces cancer in another person. Indeed, at the population level, there may be many combinations of causal factors for the same

disease. Some factors may be common to different combinations. For example, it may be that in one case of lung cancer, the combination of factors included genetics, exposure to air pollution, exposure to radon in the home, and smoking; while in another person, the combination of factors included genetics, insufficient dietary consumption of anti-oxidants like carotene, exposure to asbestos, and smoking.

Some characteristics of carcinogens and epidemiologic research on cancer: The following characteristics of most known carcinogens provide a framework for some of the thinking behind the design and interpretation of epidemiologic studies of cancer.

- There is typically a long induction period between exposure to a carcinogen and appearance of the disease. Thus, if a study has not allowed for a sufficient passage of time between the exposure and the disease, the result may report that there is no risk, where in fact there is a risk, but insufficient time has elapsed to make the risk visible.
- There is variability in the carcinogenic potency of different carcinogenic agents; some induce much greater relative risks than others.
- For any given carcinogen, the degree of risk due to exposure generally increases as the exposure level increases, but the shape of the dose-response curve may differ from one carcinogen to another.
- Most known human carcinogens were first discovered as such either by means of astute observation of a clinician noticing a cluster of cases among people who shared a common characteristic (such as working in a particular workplace) or by means of epidemiological research. In most cases, there was no known mechanism to explain the association at the time. Where the mechanisms have been elucidated, they were usually discovered subsequent to the epidemiologic demonstration of a causal relationship. (Siemiatycki 2014)

5.2 Bradford Hill "features"

Because of the complexities of epidemiologic research, there has been some concern with how epidemiologic evidence should be used to draw causal inferences. Various authors have written about the types of information that might be considered in assessing

whether a body of evidence demonstrates a causal relationship. A set of features, developed in the context of the Surgeon-General's Report on Smoking and Health (1964) and authored by Bradford Hill in 1965, has achieved a wide consensus in the epidemiologic community as a pedagogical guide. Hill himself referred to these as "aspects", "features" or "characteristics" of an association, and warned against treating them as "hard-and-fast rules of evidence that must be obeyed". (Hill, 1965) He deliberately avoided referring to them as "criteria."

Since Hill wrote those thoughts at the beginning of the era of modern epidemiology, without the benefit of decades of practical experience in the way those thoughts were taken up, and how they applied to issues other than smoking and cancer, it is understandable that the practice of evaluation of causality has evolved. A first observation, often overlooked, is that Hill took as a starting point for his writings that chance (or random variation) had been considered as an explanation for the smoking-cancer association and was determined to be an unlikely explanation. This explains why the statistical significance of the association is not included in Hill's list. In the historic context of 1964-1965 and the debates around smoking and cancer, this was a reasonable assumption to make, but for any other putative associations, this must be considered. Over the years, respected authors have paraphrased and updated these aspects in various ways, and this will undoubtedly continue. For instance, leading textbooks of epidemiology as well as the Reference Guide on Epidemiology of the Manual on Scientific Evidence (2011) all have different selections and formulations of Hill's guidelines.

In the light of 50 years of practical experience after these guidelines were written, and based on my practical experience of evaluating causality in many forums and on many topics, I would paraphrase (and modernize) Hill's guidelines as follows:

Strength of the association. This can be measured by different parameters, but for cancer studies, it is usually measured by the magnitude of the relative risk or odds ratio or risk ratio.

Statistical significance of the association. While this feature was not explicitly listed by Hill, it is nonetheless in practice an implicit and distinct consideration in assessing causality. If the estimated RR is quite high, indicating a strong association, but is based on

a very small study with low precision, this might be solely due to statistical variability. (For instance, when we flip a balanced coin 10 times, we do not always end up with 5 heads and 5 tails. Sometimes, by chance, we may end up with 6 heads and 4 tails. Does this prove that the coin was not balanced?) Evaluating the role of statistical chance as a possible explanation of the observed association is important. As explained above, the absence of statistical significance is not strong evidence of an absence of a real cause-effect relationship.

Dose-response relation. If the relative risk increases when the exposure increases, it enhances the likelihood that the observed association is really causal. There are some counter-examples, however, where the effect is only observed after a threshold of exposure has been crossed. There are various ways to assess whether there is a dose-response relation. As pointed out by Hill, a challenge in assessing dose-response is to establish reliable and measurable quantification of exposure. In studies of lifestyle habits like use of talcum powder products, the most common way is to estimate the RR in increasing categories of exposure metrics such as duration (years) of usage, or intensity of usage (frequency per day or per week or per month), or cumulative amount of usage (a combination of duration and frequency).

Absence of bias and confounding. There are many forms of bias and confounding that can infiltrate an epidemiologic study. The likelihood of a true causal association would be enhanced if we can confidently exclude all the plausible sources of bias and confounding as explanations for the observed findings. This guideline can also be considered as a component of a guideline to consider other possible explanations for the association.

Temporality. It is clear that the exposure should precede the outcome (i.e. the disease). To ascertain whether the cancer was a result of the exposure or the exposure occurred after the cancer onset seems like a simple thing, but sometimes it can be difficult to ascertain with certainty.

Cessation of exposure. It would add to the credibility of the association if it had been demonstrated that subjects who cease exposure to the agent experience reduced risks of disease compared with those who continue to be exposed. In practice this is an extremely difficult characteristic to demonstrate, partly because of the difficulty or even ethical

impossibility of changing people's habits for scientific experimentation purposes. But occasionally there may be a "natural experiment" wherein large numbers of people cease their exposure and the effects can subsequently be measured in an epidemiologic fashion.

Specificity of the association. It was believed that individual risk factors have specific pathological effects, and Hill posited that if we observe that a given agent is associated with many different pathologies, it increases the likelihood that these are somehow spurious observations, resting on some type of bias in the studies of that agent. In reality, this Hill characteristic has fallen out of usage in the intervening years with the demonstration that some agents can indeed provoke multiple different pathologies. Examples of agents that can cause multiple diseases include cigarette smoking, ionizing radiation and asbestos fibers.

Consistency of findings between studies (or replication of findings). Because epidemiologic research is susceptible to errors from random variability and from different kinds of study biases, it is important to establish that similar results are replicated in different studies, before accepting the apparent association as a generalized phenomenon. The generalizability of the inference of a causal relationship is enhanced when different studies also encompass different study populations in different communities. Generally speaking, the observation of consistent results in different studies adds to the credibility of an inference that there really is a causal relationship.

Coherence with other types of evidence. In the case of tobacco and cancer, it was seen that the historic trend in lung cancer mortality rates in the US and UK followed quite closely the national trends in consumption of tobacco, with a 20-year lag. This was interpreted by Hill as corroboration of the results observed in case-control and cohort studies. Epidemiologic evidence of coherence could conceivably take many forms, and the opportunity to assess coherence is something that is specific to the factor and the disease under investigation. Assessment of coherence with historic mortality trends would only be possible in the case of a factor whose exposure in the population changed quite rapidly and dramatically over time in a way that can be documented, and for which the attributable fraction of the disease due to that factor is very high. This was the "perfect

storm" of circumstances that allowed for an assessment of the tobacco-lung cancer association by means of time trend correlations.

Analogy. Hill reasoned that if a factor is somehow similar to another factor that has already been shown to be a risk factor for the disease, then it increases the plausibility of a similar impact due to that putative factor. This is such a vague guideline, with no clear implementation suggestions, that it is not often referred to and rarely implemented.

Biologic plausibility. This guideline can encompass many dimensions of information, including physiology (can the agent or its metabolites reach the organ in which the cancer occurs?), animal carcinogenesis (does the agent produce tumours in experimental animals?), cell studies that reveal mechanistic data, and other biologic information on the toxicology of the agent.

Implementing Hill's viewpoints. As Hill himself insisted, sophisticated users of these viewpoints do not use them as a formal checklist. He summarized his views as follows:

> « What I do not believe … is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question - is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect? »

The authors of the U.S. Reference Guide on Epidemiology of the Manual on Scientific Evidence (2011) clearly stated that Hill's viewpoints should not be interpreted as formal criteria, but rather are more in the nature of a memory aid to help us review the evidence about any given causal association. They stated it this way: "There is no formula or algorithm that can be used to assess whether a causal inference is appropriate based on these guidelines."

The ideas embodied in Hill's guidelines permeate our thinking about how to evaluate causality, but the operationalization of these guidelines is specific to the problem and to the expert making these determinations. I have served on many panels to review evidence of causality on one topic or another, including on several IARC Monograph panels that

reviewed evidence of carcinogenicity. The IARC process, like the others I have participated in, does not use the Hill features in any rigid formal way. Thus any suggestion that Hill's "aspects" or "features" or "characteristics" of an association should be used as a formal checklist of criteria is simplistic and wrong. To do so would contradict the opinions of experienced epidemiologists, many textbooks, the Reference Manual on Scientific Evidence, and Bradford Hill himself.

In this section, I have laid out and explained the Bradford Hill guidelines in a generic way. Below, in section 10, I will consider how these apply in the context of the talcum powder – ovarian cancer issue.

6. EPIDEMIOLOGIC EVIDENCE REGARDING TALC EXPOSURE AND OVARIAN CANCER – GENERAL CONSIDERATIONS

Following a report that talc particles were detected in tumour tissue from women with ovarian cancer (Henderson 1971) and a report from an epidemiologic study of an association between the use of cosmetic talc powder by women and the risk of ovarian cancer (Cramer 1982) there were several subsequent epidemiologic studies on the topic. By the early 2000s the issue was garnering considerable attention in the scientific community. The International Agency for Research on Cancer, the premier agency for evaluation of carcinogens, decided to conduct a review of the issue in 2006. Following that review, there have been further studies conducted on the topic.

6.1 IARC evaluation of talcum powder products

As mentioned above in Section 2, the International Agency for Research on Cancer (IARC) is the premier institution in the world for cancer epidemiology and for environment and cancer research. One of its mandates is the evaluation of the carcinogenicity of different agents with which humans come into contact. This mandate is carried out by the Monograph Programme of IARC. This is achieved through a process that involves identifying chemical or physical agents for evaluation and convening specially selected international expert panels that are mandated to review all pertinent evidence on the topic and write a thorough review culminating in an evaluation of whether the agent(s) are human carcinogens.

In February 2006, there was such an IARC Monograph meeting to evaluate some agents, including talc. The IARC Working Group comprised 16 highly respected and recognized scientists from around the world. I was asked to Chair the Working Group. We reviewed all the evidence that was available up to that point in time. This certainly included epidemiologic evidence, but it also included evidence from experimental toxicology, physiology, molecular biology and other domains. The IARC Monograph Programme has a formal system for classifying agents. At the time of that IARC review of talc, the Monograph Working Groups had to classify each agent under review into one of the following categories:

1 Carcinogen
2A Probable carcinogen
2B Possible carcinogen
3 Not classifiable
4 Not carcinogenic[2]

After reviewing the evidence on talc, the panel concluded that talc was a "possible carcinogen" (2B), based primarily on epidemiologic evidence regarding the association between dusting powders and ovarian cancer. Here is the definition of this category from the IARC Monograph:

> "Group 2B: The agent is possibly carcinogenic to humans.
>
> This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals."

This 2B categorization was based on the panel's decision that there was "limited evidence of carcinogenicity in humans", which is in turn defined by IARC as follows:

> "Limited evidence of carcinogenicity in humans: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."

[2] In 2019, IARC eliminated this category from the classification because the Monographs program has adopted the strategy of not selecting an agent for review if there is no evidence suggesting carcinogenicity. (Samet et al 2020)

Subsequent to the completion of the IARC Monograph on talc, a subgroup of the epidemiologists who were on the IARC Working Group, including myself, reviewed the evidence again, but with a view to producing a meta-analysis of the results from the most informative studies conducted to that time. This resulted in the paper by Langseth et al. (2008). This paper was not an IARC publication.

6.2 Some general considerations

6.2.1 *What were women exposed to in body powders*

Talc has been the main ingredient of body powders used by women over the past century. "Talc particles are normally plate-like. When viewed under the microscope in bulk samples or on air filters, they may appear to be fibers ... Talc may also form as true mineral fibers that are asbestiform; asbestiform describes the pattern of growth of a mineral that is referred to as a 'habit'. Asbestiform talc fibers are very long and thin." (IARC 2010) The structure of platy talc is characterized by a hexagonal sheet arrangement of silicon-oxygen tetrahedral groups in a common plane which creates a double-sheeted structure. These sheets are easily separated which accounts for the "silky" or "smooth" feel of talcum powder products (IARC, 2010). As a mined mineral, the precise chemical and physical characteristics of talc are in part determined by the particular geological formations from which it is extracted. The local conditions can also produce "impurities" in the extracted talc including asbestos, quartz and various metals. It is claimed that cosmetic talcum powder products normally contain >98% talc (Zazenski *et al.*, 1995) but the purity may have been lower in the past. (IARC 2010)

Asbestos is a commercial term that comprises six minerals that occur in the asbestiform habit: actinolite, anthophyllite, chrysotile, grunerite, riebeckite and tremolite. Apart from chrysotile, the other types of asbestos can occur in a non-asbestiform habit, just as talc can occur in both a non-asbestiform and asbestiform habit. Some types of asbestos are found in the same geological formations as talc. (IARC 2010)

By the 1970s it was reported that asbestos fibers were found in commercial talcum powder (Cralley 1968; Rohl 1976), though there was some doubt expressed regarding the quantification of the exposure and the ability to discriminate between asbestiform and non-asbestiform talc. (Krause 1977; IARC 2010) The talc industry was constrained to

remove asbestos from talcum powder products. Representatives of the talc industry have claimed that talcum powders have been free of asbestos and fibrous talc fibers since the 1980s, but this assertion has increasingly come under doubt as a number of labs have reported finding asbestos fibers in talcum powder products. (Paoletti 1984; Blount 1991; Gordon 2014; Longo 2018; Longo 2019) These various studies that have reported finding asbestos in historic talcum powder samples have been challenged by CIR 2013 and by Anderson 2017. These various findings and opinions are somewhat complicated by the fact that both talc and asbestos have varied chemical and physical characteristics and various methods can be used to measure them. Nonetheless, it appears that talc powder contained asbestos for many years after it was claimed to have been removed. There is evidence of asbestos in talc from studies and testing performed by J&J, FDA, and consultants who tested historic samples of JBP over 4 decades.

Asbestos, and all forms thereof, has been evaluated to be carcinogenic. It has long been recognized that inhalation of asbestos carries with it a risk of lung cancer and of mesothelioma, a cancer of the lining of the lungs, as well as larynx cancer. What has only been recognized in the early 2000s is that women who are exposed to asbestos experience an excess risk of ovarian cancer. (Straif 2009; IARC 2012) This conclusion was based on five studies; a subsequent meta-analysis reported that the RR of ovarian cancer among asbestos-exposed women was highly statistically significant 1.77 (1.37-2.28). (Camargo 2011) The route of exposure that generates risk of ovarian cancer among women exposed to asbestos is not clear; however inhalation and migration of asbestos particles to the ovaries is a credible biologically plausible mechanism. (Miserocchi 2008)

Among the metals detected in talcum powder products are some which are recognized carcinogens, namely nickel and chromium. The extent of the contamination of talcum powder products by these metals, during the entire period of commercial production of talcum powder products over the past several decades, is not known. Nor is it known how these exposures measure up to the exposure levels to these metals that may cause cancer. However, evidence that asbestos and some other known carcinogens have been detected in some commercial cosmetic talcum powder products and credible mechanisms that such particles can translocate to the ovaries are considerations in deriving an opinion on

biological plausibility, and I will consider these below in my discussion of biological plausibility of a causal link between talcum powder products and ovarian cancer.

Alternative formulations of baby powder include cornstarch formulations, which have become available in the past 40 years. Both talc-based and cornstarch-based powders have been on the market over this period of time.

6.2.2 *Types and routes of exposure and ascertainment of exposure information*

Body powders can be used on different parts of the body and can result in exposure via different entryways to the body. Among common types of usage are: on the perineum, on feet, on underarms, on sanitary napkins, on diaphragms or combinations of these, or "all over" or via use by male partners on condoms, and so on. Among women who used powders, there can be an enormous range of usage from a few occasions in a lifetime to profuse daily usage. Among the many dimensions of talcum powder exposure that might influence the risk of cancer are the following: manner in which the talc was applied, age at which exposure began; if it ended, age at which it ended and years since it ended, frequency of use per day, week or per month, multiple applications including to genitals, undergarments, sanitary napkins, etc., and whether and how usage varied at different ages.

In the case of exposure to cosmetic talc powder, the most common and practical way of ascertaining exposure in an epidemiologic study is to question women. There are many ways this can be done, and indeed many types of questionnaires have been used in epidemiologic studies. A very simple format that has been used is to ask a question such as "have you ever used powders on your body?" But, the validity of the response might be enhanced if the question is framed in a manner that gives a clearer explanation of what the investigator means by "ever used" and by "on your body". An example of a more pointed question would be: "Have you ever used powders that contained talc on your genital area more than once a week for at least 6 months of your life? This would include powdering your genital area directly or powdering your underwear or powdering your diaphragm or powdering your sanitary napkin. If yes, at what age did you begin? At what age did you stop? How often did you do this?" The challenge for the researcher is to strike the right

balance in formulating questions, between simplicity of the question and clarity of what the question means.

There are scores of ways such questions can be asked, and there has been great variability in the methods of questioning among the different studies of powder use and ovarian cancer. In most studies, the questionnaire question about Ever Use was actually about Ever Regular Use, not Ever Occasional Use. Further, information on duration and amount of usage can be detailed or cursory. Some studies have used a single simple question, while others have used scores of questions to get at the lifetime history and many facets of powder use. Even if detailed information is collected on the questionnaire, this does not necessarily mean that the investigator will analyze and report results in relation to every permutation of possible usage patterns. It might just create a lot of "visual noise" to do that, and it would usually be discouraged by journal editors.

6.2.3 *Outcome variable – ovarian cancer*

Ovarian cancers can be diagnostically classified in different ways according to cell type and invasiveness of the tumor. *A priori*, it is not known whether a risk factor affects all subtypes of ovarian cancer or only certain ones, and even if it does affect all types, whether it affects all types equally. Thus, it is in theory desirable to examine risks in relation to each type of ovarian cancer. But there are two practical impediments to this *desideratum*. Depending on the source of clinical information, the epidemiologic investigator might not have access to information on the subject's type of ovarian cancer. The second impediment is one concerning statistical power. When information is available to an epidemiologic investigator regarding these dimensions of classification of the tumour, there is a trade-off in statistical power between "lumping" all types of ovarian cancer and "splitting" into different subtypes which might produce uninterpretable and undesirable "visual noise".

7. META-ANALYSES REGARDING TALCUM POWDER PRODUCTS AND OVARIAN CANCER: MY PROCEDURES

In the context of this legal action, my mandate is to review all relevant scientific evidence available to date, in order to provide the court with my opinion regarding the link

between talc powder exposure and ovarian cancer. The methodology I employed is the same one I have used in my career as an internationally recognized researcher.

Table 1 lists the components of the process I undertook to accomplish my mandate.

7.1 Information consulted for the present review

I carried out an up-to-date review of the scientific literature, primarily the epidemiologic literature, concerning the association between use of talc powder and risk of ovarian cancer. In fact, this was built on a platform of information I had acquired initially as a result of participating in the 2006 IARC review of talc, and then up-dated in 2017-2018 when I was involved as an expert in a US court case regarding the risk of ovarian cancer following exposure to talcum powder. In preparation for formulating my opinions in that case, I assessed, researched, reviewed, and consulted a large number of documents.

Since my involvement in that case, I have maintained an active interest in the topic and I have continued to scan the scientific literature for newly emerging publications. Cumulatively, the documentation I have considered includes, but is not limited to: the IARC Monograph Programme on talc, which reviewed all informative evidence that had been published before 2006,[3] all original epidemiological studies published on this topic, all meta-analyses and opinion pieces, and review papers or reports on experimental toxicology, molecular biology, and mechanisms of talc toxicology. While I considered evidence from toxicology research, the central focus of my review has been on the epidemiologic evidence. I systematically reviewed the lists of references of all relevant studies referenced in the reports at my disposal to identify yet more relevant publications on talc and cancer. I recently conducted a Pubmed search and this did not produce any new informative publications that had not already been identified. A complete listing of the publicly available documents that I consulted for the present report, as well as references cited explicitly in this report, is provided in the **Bibliography**.

[3] Note that although the IARC publication on talc was published in 2010, the meeting on which it is based was held in 2006.

7.2 Selecting studies for inclusion in reviews and meta-analyses

For the purpose of preparing this report, my first task was to find the relevant publications and to set out the distinct pieces of epidemiologic evidence, namely the results of different studies. A meta-analysis should focus on original results in published studies, and should not include opinion pieces, reviews, and previous meta-analyses. After eliminating those, I reviewed each paper that presented original results and I excluded the those that I judged to be uninformative for a meta-analysis of talc and ovarian cancer, namely: Eltabakh 1998 (cases were peritoneal tumours and controls were ovarian tumours); Hankinson 1993 (no numerical results presented); Jordan 2007 (benign tumours only); Langseth 2004 (not based on perineal application of powder).

Appendix A provides a list of 40 publicly available publications that have included some original results that pertain to the association between powdering and ovarian cancer. The appendix shows which publications were included and which papers were excluded from my main meta-analysis. For each of the 21 excluded papers, the table also shows the reason. The primary reason for exclusion was that the results presented therein were subsumed by a subsequent publication by the same research team or as part of a pooled analysis of multiple studies.

Appendix B1 and B2 shows the 24 studies that were ultimately included in the main meta-analysis or in one of my meta-analyses, and brief descriptions of the administrative and contextual features of each study (Appendix B1) and the variables used in the analyses (Appendix B2). Most studies were conducted in the USA. Most were case-control studies and of the case-control studies, all but four used some type of population control series. Most studies had fieldwork data collection in the 1970s and 1980s; only a few studies started data collection after 2000.

Different studies had different questions in the questionnaire regarding talc powder exposure and different studies reported different variables. The questionnaires usually elicited lifetime use that was more than very sporadic, with terms like “regular” use. The Gonzalez 2016 cohort study failed to ask about lifetime exposure before the interview; they asked about usage only in the preceding 12 months. The Gates 2010 paper was based on the NHS cohort Study which asked about the use of talc up to 1982 but not

afterwards. Indeed, it was typical in the cohort studies to collect the information about talc exposure at the baseline of recruitment of the woman and to not obtain any subsequent information on talc powdering behaviour. The tacit assumption of such a procedure is that the woman's powdering behaviour did not change over the years or decades of follow-up. Some studies asked separately about different routes of exposure and then rolled them together in statistical analyses, while some rolled all routes of exposure together in their questioning. The term that I show in Appendix B2 is the term that the authors reported in their publication of results; it is sometimes rather cryptic. Appendix B2 also shows the variables that the authors reported having used as adjustment variables. Sometimes these are variables that were explicitly included in final statistical models, and sometimes these were dealt with in a more indirect way such as a staged analysis in which a screening is conducted using a change-in-estimate procedure.

7.3 Extraction of RR results from all informative publications

Each publication typically contains multiple results regarding powdering and risk of ovarian cancer, depending on such considerations as the type of ovarian cancer, route of exposure, the metrics of exposure and the subsets of the study population. For instance, some studies reported results based on particular ways of using the powders, such as on feet or perineal use or use after bathing or use on sanitary napkins or use on diaphragms or use by male partners, and so on. And many studies just reported results for all routes of perineal exposure combined.

From the publications listed in the Appendices, I extracted all results showing RRs between talc powdering and ovarian cancer, and I had these results put into a Filemaker database. This was a value-free exercise. I made no judgement at that stage about relevance or quality of the study or the published results. It was only an attempt to lay out in one "place" the whole of the evidence and to prepare for subsequent analyses. There were over 750 results in this database. On average, each publication contained about 18 different RR results of various aspects of talc powder exposure and various types of ovarian cancer. Some contained fewer and some contained many more. (For instance, one study publication contained 180 results, with varying types of ovarian cancer and varying definitions of exposure to powdering.)

7.4 Objectives and conduct of meta-analyses

It is possible to conduct meta-analyses for different combinations of types of exposure to talc and types of ovarian cancer. The most important and widely cited object of meta-analyses is the estimate of the RR corresponding to the binary variable "Ever regular use" vs "Never regular use" and all types of ovarian cancer combined. This was the core meta-analysis. For this analysis, I aimed to use the reported results pertaining to all types of perineal use combined. Where the results were reported for individual routes of exposure rather than all perineal use combined, I identified the one that came closest to powdering in the perineal area from all routes. While this may seem like a simple tactic to implement, some studies were reported in such a way that in fact I had to make "judgement calls" about which of the reported results came closest to the desired metric. Analogously I aimed to use reported results for all types of ovarian cancer combined, and all degrees and amounts of exposure combined.

For "dose-response" assessment, I present results from all studies that showed results according to three pertinent metrics of exposure: duration (years), intensity/frequency (uses per day, week or per month), and cumulative number of applications, measured sometimes in absolute numbers or sometimes in quantiles. Of the three, the most meaningful is the cumulative number of applications. I carried out meta-analyses to elucidate the RR among women with relatively high levels of exposure.

I also conducted meta-analyses to estimate risk in relation to the most common, and most commonly reported, histological type of ovarian cancer – serous invasive cancer – and in relation to the most commonly reported pathway of perineal exposure to talcum powder, apart from direct powdering – application to sanitary napkins.

Because there were typically many results reported in each paper, and for some studies, multiple papers reporting results, it was important to respect, insofar as possible, the following operational principles:

- In each meta-analysis, each study should only provide one result, so as to avoid double-counting evidence.
- The decision about inclusion of a study result should in no way be influenced by whether or not a particular study demonstrated high risks or low risks or no risks.

There were several challenges in implementing the procedures:

- Some studies were reported in multiple publications, sometimes the same study subjects were analysed and reported in different ways and sometimes different subsets of the study population were included in different publications. Sometimes the authors fail to clearly elucidate how the data used in one of their papers overlaps with data used in another of their papers from the same study.
- Different studies used different questions about powder use in their questionnaires, and sometimes the same study reported results by different ways of asking about or defining exposure.
- A given study may have presented one result or many results, each addressing a different definition of the talc exposure variable and different way of grouping the ovarian cancer cases.
- Different studies dealt differently with the histologic sub-types of ovarian cancer, sometimes grouping them all, or sometimes separating them, or sometimes reporting both grouped and separate results for different sub-types.
- Different studies used different metrics for analysing powder exposure and estimating its corresponding RR.
- Different studies dealt differently with the challenge of adjusting powder-related risks for possible confounding by other factors.

Decisions had to be made regarding which types of exposure to consider, which types of ovarian cancer to consider, which metrics of exposure to consider and which studies and publications to consider. It is necessary to be rigorous in making such decisions ahead of time, rather than "cherry-picking" results from different studies that appear to support one theory or another.

Notwithstanding my intention to identify all unique studies and to extract a best "bottom line" result from each study, the nature of the studies and how they were analysed and reported led to many judgement calls, as mentioned above. It must be acknowledged that there can be differences of opinion among equally competent and equally well-motivated

scientists in how to choose among the different publications and the different results within publications.

One objective I could not achieve was to conduct a reliable estimate of risk separately for women who used powders based on cornstarch-based formulations as opposed to talc-based. Most epidemiological studies have not tried to ascertain whether the women in their studies used talc-based or cornstarch-based formulations and many women were probably unaware of the composition of the powders they used at different times. It is impossible to ascertain with certainty from most of the publications whether the reported epidemiologic results pertain to talc-based powders or cornstarch-based powders or both. Those studies that did report results for cornstarch had few women self-reporting use of cornstarch and the risk estimates were rather imprecise and unstable. For those studies that did report separately the findings for talc-based and cornstarch-based formulations, I used in the meta-analyses the results reported for talc-based powders. For those that did not make such distinction, I used the results combining all types of powders as reported. If in truth there is no excess risk of ovarian cancer associated with cornstarch powders but there is an excess risk associated with talc powder, the inability to discriminate the two types of powder in epidemiologic studies would have the effect of diluting the estimates of risk due to talc. That is, the RR estimates for talc would be attenuated.

While I believe there are qualitative differences between the different studies in the way talc powder data have been collected, analysed and interpreted, I have refrained from imposing my judgement about the quality of the study on the selection of studies to include in meta-analyses. Indeed, in this section, I refrain from making any critical comments about the individual studies. In later sections, when addressing possible biases and distortions, I will make some comments concerning quality of different studies.

Fortuitously, and unbeknownst to me when I first embarked on the search for relevant studies in 2017 to include in meta-analyses, three other sets of investigators (Berge et al 2018; Penninkilampi et al 2018; Taher et al 2019) were carrying out separate meta-analyses on this topic at about the same time as I was carrying out mine. This provides an opportunity to do some cross-comparison of different meta-analyses. I will comment on these after presenting the results of my meta-analyses.

All meta-analyses were conducted using the well-known package Comprehensive Meta-Analysis Version 3. Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. Biostat, Englewood, NJ 2013; https://www.meta-analysis.com/index.php?cart=BFZW2135997

I used a random effects model in all meta-analyses. As is commonly done, I extracted from the meta-analysis output the meta-RR estimate and the confidence interval, as well as the I^2 index of heterogeneity among the studies in the meta-analysis. The interpretation of heterogeneity among studies is not straightforward. In some circumstances, it might flag outlier results that may indicate questionable quality or relevance of the study in question. It some circumstances it might lead to identification of certain types of studies that provide different results from the rest, and this might lead to some understanding of which types of studies are more reliable for the purpose. And in some circumstances, it might just indicate that there are such differences in populations studied and study procedures (including exposure and outcome variables, statistical methods, and reporting procedures) that it is not really to be expected that there is a single underlying RR value that underlies all studies. In clinical research, where meta-analysis is used more regularly than in observational research, the procedures are much more standardized and homogeneous than they are in observational studies.

8. EPIDEMIOLOGIC EVIDENCE: STUDY RESULTS AND META-ANALYSIS RESULTS

8.1 Ever/Never exposure to talc and all ovarian cancers

The most general association and the most widely reported one is that between Ever/Never use of talcum powder and any type of ovarian cancer. **Table 2** shows RR results, as well as the corresponding 95% confidence intervals, for each informative study included in the main meta-analysis or in any sensitivity analyses. As I explained in Section 4.1, the single number which reflects quite well the statistical strength of a study, be it case-control or cohort, is the number of exposed cases, and I have included this parameter in Table 2. Table 2 shows the RR reported in each study by Ever (regular) use of powder in the perineal region (all routes of perineal exposure including direct powdering on genital area, on sanitary napkins, on underwear and on diaphragms). The table shows results for all types of ovarian cancer combined.

Before conducting any meta-analyses, we can peruse the results in Table 2 to observe certain patterns.

Of the 34 RR results shown in Table 2, two are below 1.0, one equals 1.0, and 31 are greater than 1.0. On the null hypothesis that there is no true association between powdering with talc and ovarian cancer, we would expect as many of the RR estimates to be below 1.0 as to be above 1.0. The observed distribution (2 below and 31 above) is clearly and strongly in defiance of the null hypothesis. Further if we rank the RR estimates from lowest to highest, the median value, the one in the middle, is 1.34.

This informal analysis does not take into account that the 34 estimates in Table 2 are not mutually independent of each other. Some are components of others. There are various ways to carve out independent sets of results from this list of results in Table 2, and the meta-analysis is designed to do that. But no matter how the studies are configured, it will be found that one or two of the RR estimates are below 1.0 and almost all are above 1.0. Such an imbalance cannot be due to chance.

8.1.1 *Strategy for main meta-analysis and sensitivity analyses*

An investigator typically has in mind a strategy for analyzing and presenting the results. There may be some judgement or assumptions involved in deciding on the strategy. The investigator may wish to see how the results would be affected if other judgements or assumptions were made. In other words, how robust are the results to alternative judgements and assumptions. Such alternative analyses are referred to as *sensitivity analyses*.

There were several dilemmas in selection of studies and results to include in the meta-analysis. I made decisions in each case that I believe provides the best basis for a meta-analysis. But in deference to other possible decisions that might have been made, I conducted some sensitivity analyses as well. I list what the dilemmas were and which options were selected for main analyses and for sensitivity analyses.

a. Terry 2013 and its component studies, and overlap with Wu 2015.

The Terry 2013 paper brought together data from 8 different research teams. Some of those teams had previously published their results on talc and ovarian cancer and some

had not. One of those, Cramer's, contributed three studies, so the Terry 2013 paper *de facto* embodies 10 studies. Normally, a pooled analysis would take precedence over the individual component studies. In this case, however, there were complicating factors. The Los Angeles component study of Terry 2013 (Wu, Pike and colleagues) was conducted in stages and the Terry 2013 pooled analysis only had access to the early stage. Subsequently, Wu and colleagues carried on with their data collection, and published a more complete set of results from their study in Wu 2015. The Terry 2013 paper contained 208 exposed cases from the Los Angeles study, whereas the Wu 2015 paper contained 701 exposed cases. In the entire Terry 2013 paper there were 2600 exposed cases. Ideally, we would wish to exclude from the 2600 exposed cases in the Terry 2013 paper, the 208 exposed cases that came from the early Los Angeles data. But that information was not available in the papers. Thus, there is an 8% overlap between the exposed cases in the Terry 2013 paper and those in the Wu 2015 paper.

I adopted the following strategy. For the main analysis, I included both Terry 2013 and Wu 2015. The 8% overlap of exposed cases is unfortunate, but I believe its impact would be trivial, and in any case, we will have some empirical evidence of its impact from a sensitivity analysis.

I conducted sensitivity analyses using a different strategy. The Terry 2013 paper contained a table in which the individual results of the 8 component studies were reported. I used the results as reported there for 6 of the 8 component studies, for which the Terry paper contained the latest results. For the Los Angeles study, I used the result reported in Wu 2015 which was much more complete than the L.A. study result in Terry 2013. The eighth study was the study of Cramer that was one of the components of Terry 2013 but that was also reported subsequently in Cramer 2016. It is not clear whether the Cramer 2016 paper contains more up to date data than the corresponding component in Terry 2013, but it possibly does.

To summarize, the main analysis contained the pooled result from Terry 2013 and the result from Wu 2015. There was a sensitivity analysis that dropped the pooled result from Terry 2013, and included the (apparent) latest published result for each of the 8 components.

b. O'Brien 2020 and its component cohort studies.

There have been four informative prospective cohort studies, of which three have published results on talc and ovarian cancer in the past. O'Brien et al 2020, in collaboration with the investigators from all four cohorts, conducted a pooled analysis of the talc-ovarian cancer association, combining all of the individual subjects in all four studies. By contrast with previous cohort study evidence, the results in O'Brien 2020 benefit from: inclusion of the NHSII study which was previously unpublished, updating of cancer incidence in all studies, and harmonized mutually agreed statistical analysis strategy. There is little doubt that the results from the O'Brien 2020 paper are superior to and should replace the results of the individual papers that were previously published from the cohort studies. This elimination applies to the following papers listed in Table 2 or in Appendix A: Gertig 2000, Gates 2008, Gates 2010, Houghton 2014, Gonzalez 2016.

There is one dilemma in relation to the use of O'Brien 2020 results in meta-analyses. Each component cohort study team collected information regarding hysterectomy and tubal ligation history of the women at baseline of the cohort constitution. The authors argued that particles of talcum powder could not possibly migrate to the ovaries if the reproductive tract is not patent (open), and that therefore it is uninformative to include women in the ovarian cancer follow-up who do not have patent reproductive tracts. Since such information was available to the investigators of the cohort studies, O'Brien et al took advantage of the opportunity to conduct two pooled analyses, one including all women, and one including only women with patent reproductive tracts. The dilemma for my meta-analysis was which of the two estimates to use. The argument for using the result from all women is that this is mainly what was done in all the other studies (i.e. the case-control studies) that are included in the meta-analysis. The argument for using the result from women with patent reproductive tracts, paraphrasing the authors, is that this probably provides a more valid estimate of the risk, since it is not diluted by the inclusion of women in whom talc particles could not reach the ovaries. I accept the authors' argument and have used the results from women with patent reproductive tracts in the main meta-analysis. I did also conduct a sensitivity analysis using the all women estimates.

c. *Schildkraut (2016)*. This was a case-control study of ovarian cancer among African American women. The fieldwork and interviewing were carried out from 2010 to 2015. The authors speculated that publicity surrounding two class action lawsuits on talc and ovarian cancer in 2014 may have subsequently induced bias in the validity of reporting of talc exposure. Consequently, in their analysis and report, they presented two sets of results, one for all women in the study, and another for those interviewed before 2014. It is impossible for me to evaluate the validity of the speculation, as it was for the authors. Consequently, I will use the results from the entire sample and those from the pre-2014 sample. I refer to the entire Schildkraut study result as Schildkraut A and the pre-publicity result as Schildkraut B.

The main analysis included Schildkraut A. Some sensitivity analyses included Schildkraut B.

d. *Shushan (1996).* This ovarian cancer case-control study, conducted in Israel, reported results on talc and ovarian cancer, but the report was quite cryptic regarding the data collection and the talc exposure variable. The main analysis excluded Shushan 1996. A sensitivity analysis included Shushan 1996.

8.1.2 *Results of my meta-analyses on Ever/Never exposed to talc powder for all ovarian cancer types combined*

Figure 1 shows the printout from the Comprehensive Meta-analysis (CMA) package for the Main meta-analysis for the association between ever regular use of talc powder in the genital area and all types of ovarian cancer combined. 19 RR results were used in the Main meta-analysis. But the Terry 2013 study represents 10 distinct studies from 8 different study teams and the O'Brien 2020 study represents 4 different studies; therefore, the 19 RR results that were meta-analyzed represent a total of 29 distinct studies. In the forest plot, I have ordered the studies in increasing magnitude of the RR estimate. As implied in Table 2, all of the RRs in Figure 1 are to the right of the null value of 1.0. The Weight column in the forest plot shows the relative influence of different studies in determining the meta-RR. As expected, the most influential studies by far were Terry 2013 and O'Brien 2020, the two papers that incorporated multiple component studies (Eight component studies in Terry 2013 and four component studies in O'Brien 2020).

The meta-RR estimate is 1.30 with a 95% confidence limit from 1.21 to 1.40. The p-value is too small to register in 2 digits. This is a very highly statistically significant result. The probability that these results occurred simply because of statistical fluctuation (i.e., chance) is vanishingly small.

The 19 RR estimates in this Main meta-analysis had a fairly low p-value for heterogeneity, 0.15, but it was not statistically significant. There was considerable variation in RR results across the studies. This might have been due to chance. But it is more likely that there really was variability among the studies because they were conducted among different populations, using different methodologies. It would be surprising if there was no variation. In the current state of knowledge, in my opinion, the best estimate of RR is the meta-estimate of 1.30.

Table 3 shows the results of the Main meta-analysis again and contrasts it with the results of four sensitivity analyses that embody alternative plausible strategies for selecting studies and selecting results within studies. Panel II represents the option of using the estimate of RR from All women in the O'Brien 2020 study. The resulting meta-RR was identical to the one from using women with patent reproductive tracts. The tactics regarding the Schildkraut 2016 and Shushan 1996 studies had no perceptible influence on the meta-RR. Using the original cohort and case-control study results instead of the two pooled analyses had a slight effect, decreasing the meta-RR estimate to 1.26. Even the lowest of these meta-RR estimates would lead to the conclusion that there is a highly significant association.

It can be affirmed, quite confidently, that the apparent overall elevated risk for women who had ever used such powders is not an artefact of chance variation. This conclusion is not new. It has been stated by the authors of previous meta-analyses. However, I believe this conclusion is based on the most current and reliable data available in Autumn 2023.

From a statistical point of view, each of the studies listed in Table 2 shows a 95% confidence interval that overlaps substantially with the confidence interval of the meta-RR estimate (1.21 – 1.40). Further, the majority of the study-specific confidence intervals include the overall meta RR of 1.30. This shows that there are few if any studies (including the cohort studies) that are inconsistent with the overall RR estimate.

8.1.3 *Other contemporaneous meta-analyses on Ever/Never exposed to talc powder for all ovarian cancer types combined*

I started to conduct my meta-analyses in 2016 and produced successive updated versions in 2018 and now in 2023. Between 2017 and 2020 there have been three other teams that have conducted meta-analyses of the association between perineal use of talc powder and ovarian cancer. These three other recent meta-analyses can be found in publications by Berge 2018, Penninkilampi 2018, and Taher 2019. The simultaneous and independent conduct of these three meta-analyses as well as my own (decribed herein), provides a unique opportunity to cross-validate the methodologies and results. It is sometimes portrayed that meta-analysis is a fairly automated procedure which should produce identical results irrespective of who carries it out. This is far from true.

A meta-analysis usually requires two preparatory steps: identifying all informative studies on the topic and identifying the relevant result from each study to include in the meta-analysis. There are judgement calls to make in making these selections, and it is not surprising that different, equally competent, investigators may make different decisions about how to identify the studies and how to identify the most relevant results.

The four meta-analyses identified more or less the same studies and in general they extracted the same result from each study; but this was not always the case. There was some variability among the four meta-analyses in the selection of studies to include and in the selection of RR results to represent each study. Concerning the completeness of my search for studies to include in my own meta-analysis, I was comforted to note that there was no study that was identified by one of the other meta-analyses that I had missed in my search of the literature.

There are two major and several minor differences between the operational decisions of my meta-analysis and the other three. One major point of discordance in procedure was how the Terry 2013 study was dealt with. Whereas I included the pooled Terry 2013 RR result and therefore excluded the individual component case-control studies, the other three meta-analyses did the opposite. There are trade-offs between these different approaches. I prefer to use the Terry 2013 pooled result for two reasons. First, a pooled analysis with a standard set of covariates and a standard statistical model is considered

superior to a meta-analysis of the components study summary results. Second, each component publication used in a meta-analysis shows a variety of results, and the author of a meta-analysis has to choose a "best" one to represent the "bottom line" from each study. In the Terry pooled analysis, it was the original data that determined how to represent each study, rather than the opinions of the meta-analysts.

The second major difference between my meta-analysis and the three others is the way that the results from the four available cohort studies were included in the respective meta-analyses. The four cohort studies were: Nurses Health Study I, Nurses Health Study II, Womens Health Initiative, and Sister Study. The other meta-analyses included the separate results from each of the constituent cohorts, sometimes combining the two NHS study cohorts. My approach took advantage of the fact that O'Brien 2020 conducted an updated pooled analysis that combined the most recent data from each of the constituent cohorts. Analogously to the advantage that the Terry 2013 paper has for quantifying RRs from case-control studies over simply analysing the results presented in disparate publications, the results in the O'Brien 2020 pooled analysis provides the best and most up-to-date representation of the results from the four cohort studies that have been conducted. My meta-analysis used the O'Brien results.

Table 4 shows the meta-RR results from each of the four meta-analyses. Notwithstanding the differences in choices and strategies of the four meta-analyses, the meta-RR results are very similar, ranging from 1.22 (95% CI: 1.13 – 1.30) in the Berge analysis, to 1.28 (95% CI: 1.20 – 1.37) in the Taher analysis, to 1.30 (95% CI: 1.20 – 1.41) in my analysis, to 1.31 (95% CI: 1.24-1.39) in the Penninkilampi analysis. These four sets of results are really quite close to each other.

The results shown in Table 4, are in the same "ballpark" as the meta-analysis previously conducted by Langseth 2008 and they are based on a larger pool of accumulated publications. This indicates that recent evidence is consistent with older evidence and reinforces the consistency of the evidence.

8.2 Meta analysis on powdering of sanitary napkins

Tables 2, 3 and 4 pertain to RRs for the combination of all routes of exposure to the perineum, including direct dusting and dusting on sanitary napkins, diaphragms,

underwear, and condoms. When such an exposure variable was not provided in the paper, I used the one that came closest, with priority to dusting on the body directly. Most studies did not report RR results for every route of exposure separately. For the studies that did so, the numbers exposed were much lower than for all routes combined and there was limited statistical power in those analyses. Of the different routes, the dusting on sanitary napkins was generally the most commonly reported route apart from direct dusting. Consequently, I assembled the data pertaining to dusting on sanitary napkins and conducted a meta-analysis of those results.

Table 5 shows both the individual studies that had results on sanitary napkin dusting and the meta-analysis result for those studies. The meta-RR was 1.08 (95%CI 0.89 - 1.31), heterogeneity p=0.09. Given the overlap between the confidence intervals between this meta-RR estimate for sanitary napkin powdering and the meta-RR for powdering the perineal area via any route (1.30; 95%CI 1.20 - 1.41), it cannot be affirmed that the result for sanitary napkins is statistically significantly lower than the meta-RR results in Table 3 for all routes of exposure; but the tendency is in that direction.

Berge 2018, Penninkilampi 2018, and Taher 2019 also meta-analysed the data on use of powder on sanitary napkins. By contrast with my results, Berge 2018 reported an RR of 1.00 (95% CI 0.84-1.16); Penninkilampi 2018 reported an RR of 1.15 (95% CI 0.94-1.41), and Taher 2019 reported an RR of 1.12 (95% CI 0.91-1.39). Since their publications do not make it explicit which studies and which results were used in these analyses, I am unable to determine the exact reason for the discordance among the four meta-analyses for sanitary napkin powdering. In any case, it certainly appears that the RR was lower for application to sanitary napkins than it was for general perineal application. The interpretation of this finding is not self-evident. The different routes of exposure may entail very different frequency and duration of exposure. For instance, whereas use of powders on sanitary napkins might involve exposure on only a few days per month, regular use on the perineal region often involves daily or near daily application. Further, the duration of use of powders on sanitary napkins would end at the age when the woman's menstrual periods end, whereas powdering directly on the body could continue indefinitely. I am unaware of any evidence that would address the question of whether

powdering sanitary napkins leads to greater or lesser delivery of talc particles to the portal to the ovary than does direct powdering on the perineal region.

In any case, irrespective of the evidence regarding sanitary napkin exposure, the results in Tables 2 and 3 clearly show an association between exposure to talc in the perineal region and risk of ovarian cancer.

8.3 Dose response – cumulative exposure, duration and frequency

An important part of the evaluation of causality is to determine whether the results display any kind of dose-response pattern. Tables 6 to 8 show results for three quantitative metrics of exposure.

Trends by cumulative exposure.

Table 6 shows results from five publications that presented results based on a cumulative amount metric. Four of the studies were based on counts of numbers of powderings, while the Cook 1997 result was based on counts of the number of days on which powdering occurred. As can be seen by perusing the column of numbers of exposed cases, the Terry 2013 results dwarf the others in terms of the statistical information they contain. The Schildkraut study, with about one-tenth as many subjects as the Terry study, nevertheless has as many subjects as the other three studies combined. The relative statistical power of the different studies is also manifested in the width of the confidence intervals.

The evaluation of the statistical significance of a trend is not a methodologically straightforward endeavour. Of particular concern is the question of whether or not the test for trend among subjects in different "dose" categories should include or exclude the unexposed category. My view is that it depends on whether or not the study results for Ever/Never exposure are part of the set of results presented by the authors. Namely, if the only result presented is a dose-response analysis, then it is appropriate to include the unexposed category as part of the study results. If the Ever/Never result is presented and then a dose-response analysis is conducted, it is preferable to maintain statistical independence of the two analyses by excluding the baseline unexposed category from the dose-response analyses. I will interpret the data from these studies in light of this interpretation of trend tests. The downside of this interpretation of significance testing for

trend is that by excluding the unexposed category, one excludes a very large slice of the study sample and it considerably reduces the statistical power to detect a trend.

The three smallest studies in Table 6 show no evidence of a dose-response pattern. However, the estimates are so imprecise, as evidenced by the very wide confidence intervals, that they are virtually uninformative regarding the presence or the absence of dose-response.

When looking at the Terry 2013 results, which assemble data from eight teams and 10 studies, the confidence limits are much tighter and the estimates of RR much more precise. The p-value for trend (excluding the unexposed group) is 0.17. Nevertheless, with a reference value of RR=1.00 among unexposed, and with point estimates of RR in four quartiles of cumulative exposure of 1.14, 1.23. 1.22, and 1.32, these results are certainly compatible with the presence of an underlying dose-response relationship. (And the test of trend that includes the unexposed group shows a highly statistically significant trend.) Note that the absence of statistical significance of the trend among the four exposed subsets is not equivalent to the demonstration of an absence of dose-response. Similarly, the Schildkraut 2016 study results, while based on only two lifetime cumulative "dose" categories with point estimates of 1.16 and 1.67, are also compatible with a dose-response pattern.

While the various studies used different metrics to measure cumulative exposure and different categories to present them, I conducted a meta-analysis of the RRs in the highest category of cumulative exposure as reported by the authors and transcribed in Table 6. This analysis shows that in the category of women considered most exposed in each study, the meta-RR was 1.39 (95%CI: 1.23 – 1.57).

Trends by duration of exposure

Table 7 shows the results of those studies that presented RRs by duration (years) of use. The Terry 2013 pooled analysis did not report results by duration of use; however, some of its constituent studies did so and are included here. The numbers in each of the duration categories in each of these studies is quite small, and consequently the RR estimates are very imprecise, with wide confidence intervals. The categorization of duration differed quite a bit among the studies and it is not easy to compare results

between studies. There is no indication of a dose-response relationship in these results. Though the wide confidence intervals make it impossible to affirm that there is evidence against dose-response. Further, the largest study showing results by duration of use, Wu 2015, did find a significant increase in risk with increasing duration of exposure.

Analogous to the meta-analysis conducted on cumulative exposure, I conducted a meta-analysis on duration of exposure by using the highest category of duration that was reported by the respective authors. The Terry 2013 paper did not report on RR by duration, so I reverted to the publications from those component studies of Terry 2013 that did report such information. This explains the inclusion of some studies that had been excluded from the Ever/Never binary analysis of Table 2. This analysis shows that among those in the longest duration of exposure category, the meta-RR was 1.24 (95% CI: 1.07 – 1.45).

Trends by frequency of exposure.

Table 8 shows results of those studies that reported by frequency of usage. This ignores duration of usage. Like the results in Table 7, the results in individual studies are based on rather small numbers and they entail imprecise estimates of RR. Also, like Table 7, the pattern of results is equivocal. There is no clear evidence for or against an underlying dose-response.

Analogous to the meta-analyses conducted on cumulative exposure and duration of exposure, I conducted a meta-analysis on frequency of exposure by using the highest category of frequency that was reported by the respective authors. The Terry 2013 paper did not report on RR by frequency, so we reverted to the publications from those component studies of Terry 2013 that did report such information. This explains the inclusion of some studies that had been excluded from the Ever/Never binary analysis of Table 2. This analysis shows that among those with the relatively highest frequency of exposure, the meta-RR was 1.39 (95% CI: 1.24 – 1.56).

Dose-response trends reported by other meta-analysts

The Berge 2018 paper considered dose-response trends by duration of usage and by frequency of usage, analogous to my Tables 7 and 8. However, they actually fitted continuous variable models by making various assumptions regarding the amounts in

each reported category. They found that there were significant trends in risk by duration and by frequency of exposure. They did not examine trends by cumulative exposure, and in particular, they did not use the results from the Terry 2013 pooled analysis, which in my view is the most informative evidence available on dose-response.

Penninkilampi 2018 looked at risk according to long duration of usage and found no trend. They also looked at cumulative exposure with total number of applications, and they reported a slightly higher RR for women with greater than 3600 applications (RR=1.42) compared with women who had fewer than 3600 applications (RR=1.32). I cannot determine from the paper which studies were included in this analysis and, in particular, whether the pooled Terry 2013 dataset was included. The Taher 2019 paper looked at risk by duration of exposure, but they only identified two studies with a RR estimate for over 20 years exposure, whereas I identified over 9 such studies.

As indicated above, all other things being equal, the best metric of the three quantitative ones is the cumulative exposure metric, and that is the one that happens to provide the most statistically reliable data. Thus, the evidence from Table 6 overrides the weaker evidence from Tables 7 and 8. The evidence from the Terry 2013 paper is the most important piece of evidence we have on dose-response. The evidence from the Terry 2013 paper is compatible with the presence of a dose-response relationship between use of powder and ovarian cancer. Further, the meta-analyses of highest categories on cumulative exposure, duration of exposure and frequency of exposure are all compatible with an underlying dose-response pattern.

A final piece of corroboration of dose-response comes from a recent paper by Woolen 2022. They identified those studies that had reported RR of ovarian cancer by frequency of usage of talc and they extracted the RR result among the women with the highest reported frequency in each study. They conducted a meta-analysis using those "high frequency" women. Not surprisingly, the studies they identified and the results they extracted were almost identical to the ones I identified and analysed in my presentation of "high frequency" users, and that are shown in my Table 8. The resulting RR in my analysis was 1.39 (95% CI: 1.24-1.56) whereas that reported by Woolen 2022 was 1.47 (95%CI:

1.31-1.55). These are for all intents and purposes identical, and confirm that these two completely independent analyses led to the same finding.

Complementing the finding that women with higher frequency of exposure experienced higher risk of ovarian cancer (my Table 8 and Woolen 2022), I have also presented in my Tables 6 and 7, evidence that RR of ovarian cancer displays dose-response patterns as a function of duration (years) of usage of talc, and most importantly as a function of total cumulative usage of talc.

8.4 Ever use of talc and histologic subtypes of ovarian cancer

Some authors have proposed that the different types of ovarian cancer may well have different etiologies and risk factors, and consequently, there would be a clear advantage to segregating the evidence by type of ovarian cancer and evaluating the evidence for each subtype.

Most studies that provide results on RR between talc powder and ovarian cancer provide results for all types of ovarian cancer combined. Less than half of the published studies have also provided results of the associations between talc powder exposure and various subtypes of ovarian cancer.

The serous-invasive subgroup comprises over half of all cases, and the rest are split among several other histology-behaviour subgroups (mucinous, endometroid, clear cell, others, and these can be further subdivided by invasive or borderline). Those latter subgroups entail very small numbers each and barely provide enough data, in most studies, to produce informative risk estimates. **Table 9** shows the RR estimates for the main histologic subtypes as derived in the two large pooled studies. Aside from serous tumours, the others have very small numbers of exposed cases and very imprecise estimates of RR.

There is no strong consistent pattern indicating that one subtype of ovarian cancer has higher risk than another. Of course, there is variability in point estimates of RR, but on the one hand the variability in RR estimates between ovarian cancer subtypes within studies is not greater than would be expected from chance variability (mostly, the confidence limits overlap considerably), and on the other hand, from study to study, it is not always the same subtype that seems to have the highest or lowest relative risks.

Consequently, and because there were multiple studies apart from Terry 2013 and O'Brien 2020 that presented results for serous tumours, I conducted a meta-analysis for serous/invasive ovarian cancers, but not for other subgroups.

Table 10 shows all the studies that reported results concerning the link between talc exposure and serous tumours. There were 8 informative studies, including Terry 2013 and O'Brien 2020, which carried by far the most statistical weight. The meta-RR estimate for serous tumours was 1.26 (95% CI: 1.13- 1.40). This is very similar to meta-RR for all ovarian tumours, albeit based on a smaller number of informative studies. That is, with such a tiny difference in RRs between that for all ovarian cancers combined and that for serous invasive ovarian cancers, it can be inferred that the RR for other types of ovarian cancer (the complement of serous invasive) would not be far from the overall RR of 1.30. Thus, there is no persuasive evidence in these studies, taken as a whole, that the effect of talc differs by histologic subtype of epithelial ovarian cancer.

8.5 Recent evidence from other epidemiologic studies on talc and ovarian cancer

My presentation to this point has focused on the results and implications of a large number of studies and papers that presented estimates of the relative risks of ovarian cancer among women who had used talc powder in the perenial area. I synthesized that body of evidence by means of meta-analyses. I also showed results of some other published meta-analyses conducted at about the same time, and showed that notwithstanding some differences between them, all of these meta-analyses came to approximately the same conclusion of a highly statistically significant RR of about 1.30 for ovarian cancer among women who ever used talc powder. There have been some epidemiologic studies, particularly recently, that have generated evidence whose objective is not to directly estimate the RR of ovarian cancer among talc powder users, but that nevertheless help to interpret or appreciate the available evidence on talc and ovarian cancer.

Leung (2023). This is a case-control study of risk factors for ovarian cancer. This paper is not listed in Table 2 and was not included in my meta-analyses because the exposure

variable was not perineal exposure, as in all the other papers listed in Table 2. Rather, it was occupational exposure to cosmetic talc.

This study was conducted in Montreal, Canada, where cases of ovarian cancer and control women were interviewed with a wide-ranging questionnaire that included lifetime occupational histories, reproductive and hormonal factors, history of talc powder use, and many other personal characteristics. As occupational exposure was one of the primary themes that was invoked to solicit the funding of that study, it has been one of the first topics to be analysed. The methodology for analysing occupational exposures in relation to ovarian cancer involved an attempt to infer the occupational exposure histories of the women based on their histories of jobs held. This was done by means of a Job-Exposure Matrix (JEM) that had been created by the Montreal team. Applying the JEM to each woman's job history led to the assessment of exposure to a host of occupational agents. One of the occupational agents assessed in each woman's occupational history was "cosmetic talc". It was not possible to determine what the route of exposure was, but it was likely respiratory or dermal; it certainly did not involve application of talc powder to the perineal region.

The data derived from application of the JEM allowed the authors to then estimate the RR of ovarian cancer among women who had a history of occupational exposure to cosmetic talc. The result of this analysis was a RR for occupational exposure to cosmetic talc of 1.66 (95 % CI 0.80-3.46). Thus, there is an indication of excess risk, but the number exposed was too small to provide precise risk estimates. Nor did the authors speculate about possible exposure pathways of occupational cosmetic talc and the women's ovaries.

It is reasonable to question whether the Leung 2023 result for cosmetic talc should be included in the meta-analysis of the various studies that are included in Table 2, and that pertain explicitly to perineal exposure to talc. Had the result of the Leung 2023 study been added to the meta-analysis, it would have resulted in a meta-RR slightly higher than the RR=1.30 that I reported. My judgement is that the Leung 2023 result reinforces the proof of a causal association between cosmetic talc and ovarian cancer, but that it would not be appropriate to simply bundle it in with the other results on perineal exposure.

Although the Montreal study collected data on the women's use of talc powder for hygiene purposes, this data has not yet been analysed. It is up to the Principal Investigator to determine the publication strategy, in line with her obligations to the public funder of this research.

Davis 2022. This paper is based on a combined analysis of five epidemiological studies that had included large numbers of African American as well as white women, and that had entailed questioning about past use of talc powder. The objective was to assess the effect of race on the relationship between talc powdering and ovarian cancer. This combined analysis showed that overall there was a RR of 1.32 for ovarian cancer among talc users. In this set of studies, the overall RR was perfectly in line with the four meta-analysis results (including mine) shown in Table 4. Furthermore the RR was elevated in both whites and blacks who used talc powder, although it was slightly higher among whites (1.36) than among blacks (1.22).

Phung 2022. This paper is based on a combined analysis of nine epidemiological studies that had included questions about history of endometriosis as well as talc use. This paper reported that there appeared to be some effect modification, with the estimated effect of talc on ovarian cancer being stronger among women who had endometriosis than among women who had never had endometriosis.

Gabriel 2019. This paper is based on a combined analysis of three case-control studies conducted in New England and previously analysed for the association between perineal talc exposure and ovarian cancer. (Cramer 2016) The questionnaire used in the three studies included questions on douching, as well as on powdering with talc. Previously, the results of analyses on douching and ovarian cancer had not been published, but the authors were spurred to publish results on the separate and joint effects of douching and talc use by a report that indicated an excess risk of ovarian cancer due to douching but not due to talc use (Gonzalez 2016). The Gabriel 2019 paper, based on many more cases of ovarian cancer than the Gonzalez paper, reported the opposite, namely a high risk of ovarian cancer due to talc use, and no excess risk due to douching. While there is no obvious explanation for these discrepant results, Gabriel 2019 outlined a number of

plausible explanations, mainly involving limitations and flaws in the Gonzalez 2016 report.

O'Brien 2024. This paper, which appeared just days ago, presents a new and innovative analysis of data from the so-called Sisters cohort study. The Sisters study enrolled over 50,000 women who were the sisters of patients with breast cancer. The baseline questionnaire included a few limited questions about past use of talc powder and douching. Initial statistical analyses (Gonzalez 2016) showed no elevated risk in relation to use of talc (HR = 0.73; CI: 0.44 – 1.2). Surprisingly, it did indicate some excess risk in relation to douching. But this study was criticized for several limitations, including, dubious quality of information on lifetime history of exposure to talc powdering, insufficient follow-up time, and small numbers of ovarian cancer cases. Data from the Sister Study cohort were analysed a few years later as part of the pooled analysis of the four available cohort studies (O'Brien 2020). By this time, some of the limitations of the Gonzalez 2016 analysis were palliated. Periodic followup questionnaires permitted the investigators to collect more valid information on lifetime exposure to talc powdering. Additional years of cancer follow-up allowed for a more plausible latency period to be taken into account, and for a larger number of cases of ovarian cancer to accrue and be included in the analyses. The pooled analysis results indicated an excess relative risk estimate of 1.08, among all subjects, or 1.13 among subjects with patent urogenital tracts. These were the estimates that I used in my meta-analyses, as described in Table 2 and Table 3.

The unique contributions of the O'Brien 2024 paper, by contrast with previous reports and analysis from the Sister Study data, can be characterized as follows:

- Additional data was collected on women's exposure to talc in both prospective and retrospective modes. This provided a richer database from which to estimate women's exposure to talc.
- With the passage of time since the preceding analysis, many more incident cancers were accrued, which led to more statistically reliable estimates of relative risks.
- The investigators undertook the most systematic statistical attempt yet to estimate the talc – ovarian cancer association within a cohort study, while taking into

consideration some of the major methodological challenges, namely, the allegation that recall bias explains observed associations between talc and OC, the allegation of inappropriate treatment of missing data, and the impact of exposure misclassification. The authors label their methods as "a quantitative bias analysis". It can also be considered under the rubric of "sensitivity analyses". Combining the actual data collected with different "scenarios" of the magnitudes of plausible biases, the investigators found that it was unlikely that the estimated HRs for the talc -OC association were biased upwards (ie. away from the null) by the putative sources of bias that they investigated.

- In addition to addressing risks from talc exposure on OC, the investigators also estimated risks of uterine cancer and breast cancer, providing some useful context for the estimates of OC risk.

As a result of the first three enrichments listed above, they have produced a range of estimates of the talc-OC association that are much higher than what was reported in the initial Gonzalez 2016 paper. The point estimates of the RRs derived from the bias-corrected analyses were in the range of 1.17 to 3.34, depending on the posited assumptions. Furthermore, the RR estimates were higher among long-term talc users than among short-term talc users. One implication of these results is that the various previous meta-analyses on talc and OC that included the Gonzalez 2016 results (including mine presented in Table 3) produced meta-estimates of RR that were somewhat lower than they might have been, had the new O'Brien results been available. The choice of which of the new results to choose is not an uncomplicated one. To respect the court's timetable for submission of this revised report, I must refrain from embarking on a new meta-analysis that incorporates any of these new findings. Thus the rest of my report adheres to the data that were available to me at the previous submission deadline of November 2023.One new finding from these new analyses is that they imply that exposure to talc powder in the 20s and 30s may be a critical or particularly vulnerable period in a woman's life for risk from talc exposure.

As for the results concerning risks of uterine and breast cancer in the O'Brien 2024 paper, the results indicate an absence of association between talc and these two types of female

cancers. In a sense, this may be seen as evidence of the characteristic of "specificity" of an association that Bradford-Hill referred to. But more interesting in this case is the argument made in an accompanying editorial by Harris (2024) to the effect that because uterine cancer is, like ovarian cancer , a cancer of the reproductive system, it can be easily imagined that if there is a tendency for ovarian cancer cases to over-report talc exposure, similar cognitive processes might well lead to patients. with uterine cancer also over-reporting their talc exposure. Thus the absence of an association between reported talc exposure and uterine cancer is a counter-argument to the hypothesis that cases with cancers of the reproductive system have a tendency to over-report their talc exposure histories.

8.6 Summary of key bottom-line epidemiologic findings on the association between perineal exposure to talc powder and risk of ovarian cancer

Based on up-to-date data (to November 2023) and meta-analyses, the RR between ever perineal use of talcum powder products and ovarian cancer (all types combined) is 1.30 (95%CI 1.20-1.41). This result is highly statistically significant. We can rule out random variability as a possible explanation for the apparent excess risks. The point estimate would likely be slightly higher if we were able to integrate some results of the O'Brien 2024 paper into the meta-analyses.

Further, the examination of results according to the "amount" of exposure, whether measured by frequency of exposure, years of exposure, or cumulative exposure, shows that the higher the exposure, the higher the risk.

Such a pattern of findings can have only two possible explanations: it must be the result of some sort of bias or confounder that operated in multiple studies or it must be the result of a real causal association. As I will show in the next sections, the most likely explanation for this set of results is the presence of a true causal association.

9. MISCONCEPTIONS AND POSSIBLE BIASES

In reaching my opinions, I have objectively examined the data and scientific literature and considered the points of view of others who have expressed varying opinions. There are generally two sources of disagreement: misconceptions of epidemiologic or statistical

concepts which I address below in Section 9.1 and judgement of the likelihood of errors and biases in the various epidemiological studies, which I address in Section 9.2.

9.1 Some prominent misconceptions in reviewing the evidence

Table 11 lists some prominent misconceptions, and I will address them here.

Misconception 1: "Cohort studies are more valid and informative than case-control studies."

As can be seen in Table 2, the case-control studies tended to produce higher RR estimates than the cohort studies. It has sometimes been claimed that cohort studies are more valid than case-control studies. There is no theoretical or practical reason why such a blanket assertion should be universally true. There are many factors that influence the validity of a particular result in a particular study and it cannot be reduced to any simplistic assertion that cohort studies are more valid than case-control studies, or vice versa. In the next section, I will go through a number of potential sources of distortion of results from epidemiologic studies, and I show that some of them might occur in cohort studies, some in case-control studies, and some in both. Some of these distortions very likely occurred in some or all of these studies that provide data on talc and ovarian cancer. On balance, I believe the results of each of these case-control studies concerning female use of powders and ovarian cancer are credible, and perhaps more so (for reasons given in section 9), than the analogous results of each of these cohort studies.

Misconception 2: "Hospital-based case-control studies are more valid and informative than population-based case-control studies."

In a case-control study, the design objective is to define a study base, or a population base, in which the cases might occur, and to identify representative samples of cases and of controls in that study base. The purpose of a control group is to provide an estimate of the prevalence of exposure to the factor under study in the base population that gave rise to the cases. In many instances, the best source of controls for case-control studies is a population list of some sort. But sometimes using a population list is not feasible or desirable, and an alternative can be to select controls from among hospital patients with conditions other than ovarian cancer. This was done in some of the ovarian cancer case-control studies.

It is generally claimed that population-based case-control studies are more valid than hospital-based case-control studies. In fact, neither this nor the opposite statement is universally correct. Validity of a case-control study depends on the specific design features and circumstances of the study.

It is possible that some types of hospital controls have patterns of usage of powders that are different from those of women in the general population, either because the powders are actually causally associated with the diseases that those women have or because their disease or condition that led them to be hospitalised induces some women to take up the use of such powders. If such a mechanism was present in a hospital-based case-control study, it would likely lead to an artificially attenuated RR.

Misconception 3: "Counting the number of statistically significant results is a valid way of assessing consistency of results among multiple studies."

This misconception, manifested in the tone of the reviews by Goodman 2020 and Lynch 2023, betrays a lack of understanding of statistical significance. As can be seen in Table 2, several of the individual studies listed in my meta-analysis did not find a statistically significant increase in RR. This has been cited by some as evidence that there is no real causal link.

In fact, meta-analysis is a method that was developed precisely because counting significant results is an invalid way of synthesising knowledge. Namely, a result from a single study may fail to achieve statistical significance either because there is no risk in that study, or because the statistical power of the study was limited, or because of sampling variability. Meta-analysis was developed in order to combine evidence from multiple studies that may be under-powered on their own, but when combined might show a statistically significant effect. The meta-analysis cannot conjure a statistically significant meta-RR if the individual study RRs do not systematically lean in the direction of an excess risk. In the area of talc and ovarian cancer, the Odds Ratios definitely lean in the direction of an excess risk, to a degree that cannot be explained by random fluctuation.

Misconception 4: "You cannot prove causality with an RR less than 2.0."

There is nothing in epidemiologic theory or practice that justifies such a statement. Indeed, this assertion about an RR $\geq$ 2.0 threshold does not exist in epidemiology. There

are many well-established causal relations where the RR is less than 2.0. **Table 12** lists a number of such examples. In clinical medicine also, it is very common to strive to find therapies that reduce the risk of death from some disease by as little as 10%, and several such discoveries are well documented and have been integrated in medical practice, even though the change in risk is small. This is equivalent to accepting an RR of 1.10 as proving causality.

Misconception 5: "If a product has been used for a long time it must be safe."

It has been argued that since talc powder has been used for many decades by millions of women (and men and children), it has stood the test of time and should be considered safe. This is a specious argument.

Most agents in our environment or in our lifestyle which are now considered dangerous were used for decades or centuries without falling under a cloud of suspicion. These include such factors as cigarette smoking (many cancers and cardiovascular disease), asbestos (lung cancer), sunlight (skin cancer), ingesting very hot liquids (esophageal cancer), and many others.

Misconception 6: "Government agencies provide the most reliable and authoritative statements regarding the lack of carcinogenicity of talc."

Various national and international agencies have websites which list carcinogens. Examples are: National Cancer Institute (NCI), National Toxicology Program Report on Carcinogens (NTP-RoC), International Agency for Research on Cancer (IARC). It can be argued that these agencies, which undoubtedly have scientific credibility, would not put on their websites information that is out of date or invalid. However, that claim is false.

IARC has a rigorous evaluation process which is considered quite authoritative throughout the world. But the evaluation is carried out at a certain point in time. The last time talc was evaluated by IARC was in 2006. Based on the evidence available then, the panel rated perineal use of talc-based body powder as a "possible" carcinogen. Additional evidence has been accumulated and come to light since then, but there has not been a new evaluation of talc by IARC. (There are potentially thousands of agents to evaluate, and IARC has resources to only evaluate a few each year. Thus, they cannot keep re-evaluating the same ones as soon as new evidence is published.)

National Toxicology Program Report on Carcinogens (NTP-RoC) is a U.S. congressionally-mandated program to periodically publish lists of known and suspected carcinogens. Unlike IARC, it appears that the people who make the decisions are internal NTP-RoC scientists, rather than external experts, with advice from outside experts. Also, unlike IARC, the biennial reports only contain listings of those agents that have been deemed to be definite or likely carcinogens, so there does not seem to be a statutory listing of all agents that have been considered. From the minutes of a meeting of the Board of Scientific Counsellors of NTP held in 2000, it appears that the issue of talc carcinogenicity was deferred. I am not aware that the NTP-RoC has conducted a subsequent review of talc; although, when renominated in 2004, NTP deferred to IARC.

The U.S. National Cancer Institute (NCI) provides a website for medical doctors which indicates the known risk factors for each type of cancer. Based upon my understanding, they do not carry out a rigorous evaluation along the lines of the IARC evaluations or even the NTP evaluations. It is a rather superficial process compared with the IARC process and it depends on the existing knowledge of the committee members which in a short time opines about possible associations between each of the scores of cancer types and scores of potential risk factors. This is not to argue that the members of these committees have less expertise than the members of the IARC committees, but the NCI committee members have a short time (apart from their main jobs) to review hundreds of possible factor-cancer associations, whereas the IARC committee members have weeks to review just a few.

Scientists and public health agencies regularly consult the IARC evaluations and those of the NTP. The NCI website for doctors is not considered an up-to-date and cutting-edge source of information for scientists. This is, of course, no reflection on the gravitas of the NCI as a whole, which has much more invested in its original research mission than in its website for doctors.

There are other organizations which may put some information about causes of cancer on their websites. Importantly, I have not seen any agency or organization, including the FDA, that conducted a rigorous evaluation of the epidemiologic and non-epidemiologic studies like we did at IARC in 2006.

Misconception 7: "*A biological mechanism must be proven before we can establish causality*"

The demonstration of a proven biologic mechanism is not a prerequisite for demonstrating that an agent is a human carcinogen. Reliable empirical epidemiologic evidence of an association is sufficient for demonstrating causality; the demonstration of a credible biologic mechanism enhances the degree of proof, though that often lags decades behind the general recognition of causality.

There are innumerable examples in medical history of discoveries of risk factors or treatments that did not require knowledge of the mechanisms of pathogenesis in order to determine causality.

Very often, the initial suggestion of causation was met with scepticism from the vantage point of biologic plausibility. In fact, very seldom have the essential features of biologic mechanisms been worked out by the time the epidemiology has convincingly demonstrated that the association is causal. This can be asserted for the early discoveries such as the cancer-causing effects of certain chemicals in dye production facilities, certain metals in various heavy industry facilities, certain emissions of combustion of fossil fuels, ionizing radiation, and even cigarette smoking. In most of these examples, it was decades after the epidemiologic evidence became convincing that credible mechanistic theories were proven. In fact, for some, the biologic mechanisms remain unknown to this day.

Indeed, in the guidelines of the IARC Monographs, it is stated that if there is "sufficient" evidence of a risk of cancer from epidemiologic studies, then irrespective of the evidence from animal experimentation and other biologic evidence, the agent in question should be considered a Group 1 carcinogenic agent.

It is not my opinion that we should ignore or set aside consideration of biologic plausibility. As Hill (1965) indicated in outlining the thought process for establishing causality, biologic plausibility is one of the dimensions to be considered. But he also cautioned that, "this is a feature I am convinced we cannot demand". In his article, he went on to point out examples, just as I have done, where causal associations were identified and proven well before the causal mechanisms were elucidated. Thus, as I have done in other contexts, in regard to other putative carcinogens, I believe it is legitimate to

draw causal inferences about talc carcinogenicity irrespective of whether a causal mechanism has been proven.

Misconception 8: "Bradford Hill viewpoints comprise a checklist of necessary conditions"

As I explained in section 4.2, the "aspects" or "viewpoints" that Hill listed are not "criteria" and they are not necessary. This point has been made and is widely accepted by epidemiologists. The list of "aspects" in Hill's original paper have been rephrased and reworked in many textbooks and by most agencies that refer to them. They provide a loose framework, not a checklist.

9.2 Alternative explanations – Biases and errors

Before inferring that the strong statistical evidence linking talcum powder with ovarian cancer reflects a causal relationship, I considered alternative explanations for these observations. In this section I will consider a number of potential sources of distortion of the risk estimates. Some of the potential sources of distortion are unique to cohort studies, some are unique to case-control studies, and some can affect both types.

9.2.1 *Bias due to non-response or non-participation*

This is a potential source of bias in case-control studies.

Among all potential cases and controls who meet the study's eligibility criteria, some participate and some do not. The most common reasons for non-participation are refusal and the inability of the researchers to contact the person because they moved or are too sick, died or are otherwise unavailable. If access to the subject is via the treating physician or medical staff, there could be obstacles at that level. If the factor under study, hygiene powder use, is correlated with the likelihood of participation and if the participation rate is low, this could lead to biased estimates of RR. Such bias could artificially inflate or deflate the RR depending on how the various variables are related to each other. If participation rates are low, say below 70%, and differential both by case-control status and by exposed – non-exposed status, this could lead to biased RR estimates. For such a bias to explain the outcomes seen, it would require quite strong associations between likelihood of participation and powder use, and quite strong differences in such associations between cases and controls. In my opinion, it is very unlikely in the context

of these studies that response rate differentials would be great enough to induce such large bias.

9.2.2 *Recall or reporting bias*

This is a potential source of bias in case-control studies.

Because the exposure history is collected retrospectively, it is subject to both non-differential recall errors (see below), and to recall or reporting bias between cases and controls. Cases and controls may have different motivation and proclivities to recall and report use of powders. If it were true that cases had a greater tendency to over-report powdering history or if controls had a greater tendency to under-report powdering, then this would lead to an artefactual exaggeration of the RR.

There are a few possible causes of such differential reporting. First, it might be hypothesized that there is a general tendency for cases in case-control studies to acknowledge behaviours or exposures with much greater frequency than controls just because they are more invested in the research than are controls. They may wrack their brains during the interview to find instances of the queried behaviour or exposure to which controls do not pay much attention during the interview, because the controls just "want to get the interview over with". If this were the case, we would systematically see elevated RRs from case-control studies for all manner of variables in all kinds of studies. But in my experience, this does not occur. (I have conducted many case-control studies, each study eliciting information on many lifestyle factors and exposures. It has not been the case that cases systematically report more exposures than controls.)

Furthermore, and more pointedly, if such a phenomenon were operative in these case-control studies of ovarian cancer, we would see elevated RRs when women were questioned about the use of powders on other parts of their bodies than the perineal area. In fact, several studies did ask such questions. In the Terry 2013 pooled analyses, based on very large numbers of women, the overall RR for ever use of hygiene powder on non-genital areas of the body was 0.98 (0.89-1.07), in stark contrast to the analogous RR result for genital use of talc: 1.24 (1.16-1.33). In other words, when questioned about powdering in non-genital areas, controls were as likely to say "yes" as cases. Clearly, there was no tendency for cases to indiscriminately report exposures more frequently than controls.

A second possible reason for such a situation to arise is if there was widespread knowledge about powdering being under suspicion for ovarian cancer. In such a situation, women who have heard about this might internalize the notion that powdering may have caused their cancer, and they might ruminate with such intensity on the notion that they might imagine that they had used powders at some point in the past. In the Schildkraut 2016 study, the authors explicitly accommodated this possibility by separately analyzing a subset of the data that had been collected before some local publicity arose regarding the talc-OC association; they found that the RR was indeed increased after publicity circulated in the community. But this phenomenon could not have affected most studies that have been conducted, because the public discussion of a talc-OC association is very recent. I doubt if more than a handful of the thousands of women interviewed in these studies would have heard of such a hypothesis before being interviewed. As shown in a sensitivity analysis in Table 3, the exclusion of the post-publicity part of the Schildkraut 2016 study population had almost no discernible effect on the meta-RR from all informative studies.

Even in the O'Brien 2024 report on the Sister Study, the investigators found that there was an association between self-reported talc exposure and ovarian cancer, but not between self-reported talc exposure and uterine or breast cancer. In that report, they also found that a range of plausible amounts of reporting bias would not result in the magnitude of RR that they found.

In my opinion recall bias is not likely to have produced the kinds of RRs we see in these studies.

9.2.3 *Non-differential (or random) error in recall or reporting of exposure to powders*

This is a potential source of bias that would affect both case-control and cohort studies, but not exactly in the same ways.

Reporting past history of activities and exposures is always subject to some degree of error; error can result from ambiguity or misunderstanding of the questions, failures of memory, or inattention. This is certainly true for history of powdering. If such error is non-differential (i.e., equally present for cases and controls in the case-control context) it has an effect on RR estimates that is rather predictable. Namely, as I explained above, it

has the effect of artifactually decreasing the RR. The degree of attenuation is roughly proportional to the degree of error or misclassification. If there really is a causal association between powdering and ovarian cancer, then we can be rather certain that the true RR is higher than what we can see in the various studies that have reported RRs.

Furthermore, we might make some reasonable inferences about the impact of reporting error on dose-response trends as well as on the overall RR. It is reasonable to surmise that the amount of reporting error is quite a bit higher for the details of past usage (duration of usage, intensity and frequency of past usage) than it is for the simple fact of usage. That is, there is less error in a woman's report of whether or not she ever used powders on a regular basis than in her report of the details of the usage, even if powdering behaviour may be a relatively stable habit. The consequence of this is that the RR based on ever/never usage (Tables 2 and 3) is less subject to artefactual attenuation than the RRs based on categorizing the duration or intensity or cumulative amount of usage (Tables 6-8). This is a possible explanation of why there has been a much clearer signal of elevated RR for ever/never usage than there has been for dose-response.

There is likely to be more measurement error of exposure to powders in cohort studies than in case-control studies, for several reasons. First, because the cohort study questionnaires attempted to broach topics that could be relevant to many types of cancer and indeed many diseases, the questions posed in the cohort study questionnaires about talc powder use tended to be much briefer and probably less effective at eliciting valid information than the questionnaires used in case-control studies of ovarian cancer. For instance, the cohort studies did not elicit information on timing or duration of past usage, and the first publication on the Sister Study did not even attempt to elicit information about use of talcum powder products over 12 months before the interview (Gonzalez 2016). Second, whereas a case-control design involves a woman looking backwards over her life from the time of incident cancer onset, thereby addressing the entire relevant period of potential exposure, the woman in a cohort study reports on her past usage as of a certain point in her life, but there may be 10-20 years subsequent in which her habits could have changed, and of which the cohort study has no knowledge. Aside from the most recent iteration of the Sister Study that collected talc exposure information after the baseline questionnaire, the women in the cohort studies were "locked into" their

exposure category at the baseline of the cohort study. If there were women who in fact started using powders after the baseline, they would be incorrectly labelled as non-users. And, if there were indeed a risk associated with use of talc powders, the risk estimate would be diluted by the incorrect inclusion of users among non-users. Accordingly, the longer such subjects are followed, the more likely such misclassification is to occur.

The age at which information is collected is a relevant consideration. In most case-control studies, the mean age of the study subjects was between 50 and 60. The mean age at baseline questionnaire in the NHS cohort study was around 40 (Gates 2010) and in the WHI it was over 60 (Houghton 2014). In each study, women were asked about their past history of powder usage. Clearly, the WHI women had a further stretch of time to consider than the women of the NHS and even of the case-control studies.

A particular form of measurement error may well have occurred in the first report from the Sister Study (Gonzalez 2016) and produced even more attenuation of RR estimates. Namely, in their brief questionnaire on talc exposure, the question was formulated to ask women about their use of powders during the 12 months preceding the interview. While exposure to talc over the past 12 months may be correlated with exposure over the entire etiologically relevant period, which might go back decades in the life of the woman, the correlation is probably weak, and this is another source of measurement error.

9.2.4 *Short follow-up periods for disease ascertainment*

This is a potential source of bias that would affect cohort studies.

In a cohort study, if the period of follow-up after baseline is relatively short, and if the latency period between exposure and cancer is long, the excess risk may not be detectable because cases that would occur after long latency have not had time to occur. If this did occur, it would lead to an artificially low RR estimate.

This could have been an issue in the early publications from the NHS Study (Gertig 2000), in the initial WHI Study paper (Houghton 2014), in the initial Sister Study paper (Gonzalez 2016). For those studies, the O'Brien 2020 paper entailed longer follow-up and therefore improved validity. In this regard, it is noteworthy that the results listed in the O'Brien 2020 paper for those component cohort studies show higher RRs than did the initial

papers from those studies. The NHSII study reported in the O'Brien 2020 paper had extremely short follow-up and therefore poor validity. The pooled results of the cohort studies in the O'Brien 2020 paper are definitely vulnerable to under-estimation of the meta-RR because of short duration of follow-up.

9.2.5 *Diagnostic error*

This is a potential source of bias that would affect both case-control and cohort studies, but not exactly in the same ways.

The diagnosis of cancer is never error-free. And details of histology and staging are even more error-prone. Further, there are trends in diagnostic criteria and methods over time, as well as in the terminology and classifications used. Thus, what we observe in these various studies of ovarian cancer represents imperfect estimates of true biologic/pathologic status. The impact of such "errors" is mainly the same as exposure measurement error, namely it would tend to artificially reduce RR estimates. Since most case-control studies start from hospital-based cancer diagnoses as the point of entry, they usually have reasonably valid diagnostic information.

In general, cohort studies tend to be more vulnerable to this source of error and bias, because disease diagnosis information is often obtained from sub-optimal sources, such as the information provided by the study subject or her family, or information obtained from death certificates. In the four cohort studies included in the pooled O'Brien 2020 analysis, there were high quality verifications of diagnostic information that had been provided by the women or their families. But such verification may not be as reliable as information coming straight from hospital pathology or oncology services. I expect that this was not a major issue here, but to the extent that it did operate, it too would have led to some additional attenuation of RR estimates, as I explained above.

9.2.6 *Initiation of powdering as a result of ovarian cancer*

This is a potential source of bias that would affect case-control studies.

It has been speculated that women with early symptoms of ovarian cancer might take up the use of powders to help with relief of their symptoms. If so, they might report that they used powders before their cancer was diagnosed and this could artificially inflate the RRs.

While the women are usually questioned about the period before their cancer was diagnosed, there could be some "telescoping" so that women who start dusting after diagnosis respond in the affirmative to the questionnaire.

In the same vein, it has been speculated that treatment for ovarian cancer might produce side effects that could be relieved by powdering. And again, it might be posited that women ignore the instruction to refer the exposure question to the time before the onset of the cancer.

If the early symptoms of ovarian cancer provoke some women to start dusting the perineum to relieve some of the discomfort, or if the treatment provokes women to start dusting, this would lead to an artefactual excess RR.

I have not found any empirical evidence to support the hypothesis that early stage of ovarian cancer involves discomfort of a nature which induces women to start using body powders. In the few datasets I have seen which describe the age distribution of initiation of powdering, there were very few patients who started in the year or two before diagnosis of the cancer. In my opinion, this is virtually a non-issue, and if it operated at all, it would only have operated on a handful of the thousands of women who were part of the various case-control studies.

9.2.7 *Confounding*

This is a potential source of bias that would affect both case-control and cohort studies.

If women who use powders are also more likely to be exposed to other risk factors for ovarian cancer, then it might distort the relationship between powdering and ovarian cancer. The direction and the degree of distortion (bias) that would be induced depends on two components: a) the true association between the confounder and ovarian cancer, and b) the association between the confounder and dusting behaviour. Thus, depending on the direction of these two component associations, the confounding can result in artificially decreased or increased RRs.

Typically, the degree of confounding is much lower than the strength of the association between the confounder and ovarian cancer. In order for a confounder to induce an artificial RR of 1.30 for dusting, it would have to have an RR much greater than 1.30 with

ovarian cancer and a fairly strong correlation with dusting behaviour. Given that the main studies have controlled for the main risk factors, I consider it unlikely that this operates. Appendix B2 shows the covariates that were controlled for in each study, and while there is some variability between studies in the list of covariates, the main known potential confounders (age, BMI or weight, parity) have been controlled for in almost all studies. It should be noted that while smoking is a well-established risk factor for many types of cancer, it is not a risk factor for ovarian cancer; thus, there is no need to control for smoking status in studies of ovarian cancer.

A thorough investigation of potential confounders was conducted by Cramer (2016); in the large database of New England-based studies, the authors explored the potential confounding effect of a host of personal characteristics including demographic, reproductive, hormonal, comorbidities, activities, and exposures. None of the covariates that they explored had any meaningful confounding effect on the association between talc and ovarian cancer.

9.2.8 *Publication bias*

This is a potential source of bias that could affect case-control and cohort studies.

This refers to the tendency for some evidence never to "see the light of day". Namely, when results are "negative" or "null", it may be that investigators never bother to submit them for publication, or alternatively, that editors refuse to publish them. This happens, most frequently, when the hypothesis under study is not particularly topical or controversial, and when the study is small. In the talc-ovarian cancer literature this would have been more likely in the pre-2000 era when there was much less scientific interest in the hypothesis linking talc to ovarian cancer. As a sensitivity analysis, I conducted a meta-analysis on the subset of studies in Table 2 that had at least 20 exposed cases. That is, I eliminated the studies from that stratum of the universe of studies that were most susceptible to publication bias. The resulting meta-RR was almost identical to those shown in Table 4. Because this has been a somewhat controversial topic in epidemiologic circles over the past 20 years, I doubt that there were large important studies with null findings on talc-ovarian cancer that went unpublished.

In their meta-analyses, Berge 2018 and Pennikilampi 2018 both showed funnel plots of the results of the different studies. These are meant to detect so-called publication bias. Both of those analyses concluded that there was no publication bias.

In summary, I consider that the observed association between talc and ovarian cancer is not an artefact due to publication bias.

9.2.9 *Summary comments regarding biases and errors*

While the results of epidemiologic studies strongly support the hypothesis of an association between perineal use of powders and risk of ovarian cancer, we must be wary of potential sources of error and bias that can distort an association before concluding that this association is causal. I have therefore gone through the plausible sources and types of error and bias that could potentially explain the positive association seen across the relevant studies to ascertain how likely it is that each type of potential bias or error was actually operative and, if so, what the nature of its impact may have been. These evaluations are based on my professional opinion as an epidemiologist having conducted, reviewed, and evaluated hundreds if not thousands of epidemiologic studies.

Of the various types of error listed, some could artificially inflate the RR estimates and some could artificially decrease the RR estimates. Some are likely to have occurred and some are unlikely to have occurred. The one that certainly occurred and that has a non-trivial attenuating effect on RRs is random exposure misclassification (section 8.2.3). As explained above, if there is a true association, then the true RR is almost certainly greater than the estimates seen in these studies and in the resulting meta-analyses. Other types of error and bias that are highly likely to have occurred are the two that are specific to cohort studies. Namely, the Nurses' Health Study papers (Gates 2010) almost certainly suffered from an attenuated RR estimate because of the compromised reference category of "unexposed" while the Women's Health Initiative paper (Houghton 2014) and the Sister Study paper (Gonzalez 2016) and the NHSII Study almost certainly suffered from a too short follow-up period (section 8.2.4). These issues would in turn have led to an attenuated estimate of RR in the pooled analysis of all cohort studies (O'Brien 2020). In my opinion, the occurrence and the possible impact of other listed types of bias and error are more speculative, and less likely. It is instructive that the O'Brien 2024 paper which

attempted to take into account various plausible scenarios of multiple sources of errors and biases, ended up concluding that the observed RR estimates were generally lower than the RR estimates derived after "correcting" for various posited errors and biases.

Consequently, in my opinion, the observed association between talcum powder products and ovarian cancer is unlikely to be explained by any methodological problems with the studies.

10. BRADFORD HILL FEATURES APPLIED TO TALC AND OVARIAN CANCER

There are no hard and fast rules or algorithms for assessing causality based on epidemiologic evidence. Since Bradford Hill's initial publication of guidelines to aid in the assessment of causality, there have been many alternative versions published in different textbooks and articles and reports. I will use a version that is listed in a widely used reference called the Reference Guide on Epidemiology in the Manual on Scientific Evidence (2011). Of the Bradford Hill guidelines, the authors of that reference stated: "There is no formula or algorithm that can be used to assess whether a causal inference is appropriate based on these guidelines." These guidelines are simply aspects that might be considered in assessing causality.

I will give my assessment of how the evidence regarding talcum powder products and ovarian cancer fits into those aspects. While there is no objective basis or scientific precedent or "scientific jurisprudence" for quantification or weighting of the various "aspects", to help the reader to understand the relevance that I attached to each "aspect" in my evaluation, I will provide an informal ranking of the importance that I attach to each aspect, in the specific context of the assessment of causality of evidence regarding talcum powder products and ovarian cancer. I will list the aspects in descending order of importance that I attach to them.

My opinions are briefly summarized in **Table 13**.

Highly important aspects in my weighting

The most important Bradford Hill aspects to consider in evaluation of causality of talcum powder for ovarian cancer are: strength of association (including magnitude and

statistical significance of RR), dose-response, consideration of biases, and consistency of findings.

Strength of the association. This can embody both the magnitude of the RR and its statistical significance. The meta-RR estimate is 1.30. That means that the best estimate from the epidemiologic literature is that women who regularly used talcum powder products in the genital area had a 30% higher risk of ovarian cancer than women who did not use such powders. This RR is in line with many well-recognized risk factors for cancer and other diseases. For example, it is well accepted now that people living in an urban neighborhood in which the air is highly polluted with particulate matter have between a 5% and a 10% excess risk of lung cancer compared with people living in a less polluted urban neighborhood. Also, it is well accepted now that workers exposed to a solvent called trichloroethylene have about a 40% higher risk of kidney cancer compared with workers not exposed to trichloroethylene. Thus, the 30% increase of ovarian cancer for women who used talcum powders is in line with many recognized risk factors. The 30% increased risk is highly statistically significant. (Note that the statistical significance of individual studies is irrelevant to the consideration of causality; it is the totality of evidence embodied in the meta-analysis that counts.) Such a high and significant meta-RR could not have occurred by chance.

Dose-response relationship. If the relative risk increases when the exposure increases, it enhances the likelihood that the observed association is really causal. In studies of lifestyle habits like use of talcum powder products, the most common way of assessing dose-response is to estimate the RR in increasing categories of exposure metrics such as duration (years) of usage, or intensity of usage (frequency per day or per week or per month), or cumulative amount of usage (a combination of duration and frequency). The most sensitive of these metrics is the cumulative amount. I evaluated the published studies reported on risks according to the different metrics. By far, the most important set of results on dose-response is that from the Terry 2013 pooled analysis of 10 studies using the cumulative exposure metric. The next most important source from a statistical weight point of view is that from Schildkraut 2016. In both of those studies, there is a clear indication of increasing risk with increasing cumulative exposure. Since the statistical power to detect a trend is less than the power to detect an overall risk, it is not surprising that the p-value for trend

does not attain the conventional 0.05 level, but it remains true that these studies support a dose-response. To bring in more evidence, I conducted a meta-analysis of the highest category of cumulative exposure in each of the five studies that analysed their data by categories of cumulative exposure. That meta-RR was 1.39 (Table 6). This evidence of dose-response is an important consideration in my assessment of causality. The analysis by Woolen 2022 of papers that reported RRs by frequency of exposure to talc reaffirmed my finding that women with higher frequency of talc exposure had higher risk.

Consideration of alternative explanations - absence of bias. There are many potential sources of bias in observational research, including in epidemiology. It is important to consider the presence of bias in each study performed or reviewed in an evaluation of causality. The possibility of bias is so multifaceted that it is impossible to reliably assign an explicit score to the likelihood of bias in a study or in a body of studies. It is also important to understand that identifying a potential source of bias is not tantamount to demonstrating that there actually is bias. In section 9.2 I have reviewed the potential role of several types of biases and errors that can bedevil such research. I concluded there that none of those factors, including reporting bias, could have caused the apparent association.

Consistency of findings between studies (or replication of findings). Because epidemiologic research is susceptible to errors from random variability and from different kinds of study biases, before accepting the apparent association as a true causal relationship, it is important to see that similar results are replicated in different studies. When these different studies also encompass different study populations in different communities, it enhances the generalizability of the inferences. Generally speaking, the observation of consistent results in different studies adds to the credibility of an inference that there really is a causal relationship. In my review of the published epidemiological studies and meta-analysis, I was impressed by the consistently elevated risk across studies. Almost all of the 30 or so studies considered have produced an RR greater than the null value of 1.0. If there really were no association between talcum powder use and ovarian cancer, we would expect to see as many RRs lower than 1.0 as higher than 1.0. The pattern we see is like flipping a coin 30 times and getting a heads 28 or 29 times. The individual study RRs are not all necessarily statistically significant, but that is irrelevant because most individual studies did not have sufficient statistical power to detect RR in the range of 1.2-1.4. It is the statistical

significance of the meta-RR, representing the combined evidence that has the requisite power, and that excess RR is highly statistically significant. I place great weight upon this evidence of causality and, here, believe it to be amongst the most important findings. The other meta-analyses (Berge 2018, Penninkilampi 2018, Taher 2019) were based on substantially the same set of original studies as mine.

Temporal relationship. Exposure should be seen to have preceded disease. It is almost a logical truism. This is the only aspect of the guidelines that Bradford Hill considered to be necessary. In all of the studies I reviewed, the information elicited about talc exposure concerned the time period before cancer onset.

Moderately important aspects in my weighting

Biological plausibility (coherence with existing knowledge). It is both conventional and natural to consider whether any putative association is biologically plausible. The notion of biological plausibility is multi-facetted. In the case of talcum powder products and ovarian cancer, it can include such issues as: how such powders have been used, female anatomy and physiology, toxico-kinetics and toxicology of talc, in vitro and in vivo mechanisms of carcinogenesis, and others.

The first thing to note about this aspect that Bradford Hill listed is that it is called "biological plausibility", not "biological proof". That is, there was never any implication that a determination of causality should rest on a demonstrated proven biological mechanism. Hill was always reserved about this aspect, insisting that it was not an essential prerequisite to establishing causality. As I have mentioned above, it has been common in the history of medicine and epidemiology for the elaboration of a validated biological mechanism to come much later than the discovery and demonstration of a causal association.

Insofar as the issue of talcum powder products and ovarian cancer is concerned, there is evidence to support a few biologically plausible mechanisms. First, with the recognition that asbestos exposure among women can increase the risk of ovarian cancer (Camargo 2011; IARC 2012) and the growing evidence that talc products may have contained asbestos fibres, it is plausible that the asbestos fibres in talc products has caused ovarian cancers. It is not only asbestos that can contaminate talc products; there is also evidence

that commercially-distributed talc powder contained some heavy metals that are themselves carcinogenic. Second, there is credible evidence that particles such as those found in talcum powder products (and its constituents and contaminants) that are applied to the vaginal area can migrate from there to the fallopian tubes and ovaries (Venter 1979; Henderson 1986; Heller 1996; Sjosten 2004; McDonald 2019) or to pelvic lymph nodes. (Cramer 2007) In addition, as has been hypothesised and partially demonstrated in the discussion of asbestos and ovarian cancer, such particles might reach the ovaries via inhalation and translocation. (Miserocchi 2008; IARC 2012) Once the particles reach the ovaries, carcinogenesis can be triggered by the inflammation engendered by the particles. (Ness 1999; Ness 2000) There is considerable evidence that inflammation is an important mechanism for carcinogenesis (Coussens and Werb 2002; Grivennikov 2010). Alternative plausible mechanisms of carcinogenicity include talc-induced oxidative stress (Buz'Zard 2007; Saed 2017; Fletcher 2018), and genotoxicity (Shukla 2009).

The fact that there are credible biologically plausible mechanisms by which talcum powder products can reach the upper genital tract causing an inflammatory response, along with the presence of asbestos fibres and other carcinogens, is a consideration in support of my opinion that the genital use of talcum powder products can cause ovarian cancer.

Aspects of lesser importance in my weighting

Cessation of exposure. It is rare that there is valid evidence available to assess the impact of cessation of exposure in an observational study. In the studies on talcum powder and ovarian cancer, there is no evidence one way or the other concerning the effect of cessation of exposure. This aspect is not applicable and I place almost no weight on it.

Specificity of the association. This aspect is premised on the notion that an agent-disease association is more likely to reflect a causal association if the agent is not also associated with other diseases. In the 1960s, this seemed like a reasonable argument. In light of evidence from the past 60 years, this argument is no longer made and this aspect has fallen out of usage with the demonstration that some agents can indeed provoke multiple different pathologies. Examples include cigarette smoking, ionizing radiation and asbestos fibers. Therefore, I do not place much stock in this aspect. Still, I note that in the case of the

Sister Study, O'Brien 2024 found that the association with talc that was observed for ovarian cancer, was not observed for uterine or breast cancer.

Analogy. Hill argued that if the agent is similar to another agent that has been shown to be a cause of the disease, then the agent under investigation is more likely to be a cause. The fact that exposure to asbestos fibers can cause cancers in lung, larynx, mesothelial tissue and ovaries (IARC 2012) can indicate that, by analogy, talc, which is similar in some respects, might be able to induce carcinogenesis. Thus, there is an argument for an analogy between talc and asbestos. While this aspect supports causality in Hill's framework, I consider it a more tenuous aspect than the ones listed above.

Coherence with other types of knowledge. Coherence with other knowledge can encompass a multitude of possibilities. This aspect is both vague and very open-ended, with no real operational instruction on how to use it. Hill gave an example in his paper, but the example was only applicable to tobacco and lung cancer. Like analogy and specificity, this is an aspect that, if it can be demonstrated, can enhance the likelihood of causality, but its absence cannot detract from causality. I do not consider it to have much weight in this context.

11. CONTRAST WITH IARC MONOGRAPH OF 2006

The 2006 IARC Monograph meeting, which I chaired, concluded that a causal relationship was "possible" between perineal talc powder exposure and ovarian cancer. I concurred with that evaluation.

It is now my professional opinion, based on the totality of the evidence currently available, that, to a reasonable degree of scientific certainty, the causal relationship between perineal talc powder exposure and ovarian cancer is "probable".

What has changed in the years since the IARC review of 2006?

Some of the largest and most influential studies have been published since 2006. This includes Terry 2013 and its component studies, Schildkraut 2016, and O'Brien 2020 and its component studies. The RR estimates in Table 2 are remarkably consistent in showing a highly statistically significant excess risk. Recently updated results from a pooled analysis of cohort studies (O'Brien 2020) has shown that, notwithstanding some

limitations of the validity of cohort studies in this area of research, the RR estimates that have come out of the cohort studies are not as discrepant from those of the case-control studies as had been reported earlier.

The number of published study results and scientific literature addressing the epidemiology, toxicology, molecular biology, and mechanistic studies has substantially increased since 2006, and the evidence of excess risk has been consistently demonstrated across the past three decades.

The various possible biases that are on the table remain substantially similar to the ones that were considered by the IARC panel. At the time, we were not convinced that the apparent excess risk could be explained by those potential biases or confounding. As stated above, my review of the relevant studies and potential biases has led me to conclude that bias does not explain the consistent increased risks seen across the credible studies.

There is important new information with regard to the issue of dose-response. Contrary to the impression that the IARC panel had of a total absence of dose-response, and even a possible trend in the opposite direction, the results of three publications, Terry 2013 and Schildkraut 2016, using cumulative exposure metrics, and Wu 2015 using duration of exposure and Woolen 2022 using frequency of exposure, all demonstrate a clear compatibility with a dose-response relationship. The recent meta-analysis of Berge 2018 supports the presence of dose-response in both duration and frequency of use. The most convincing of these is the Terry 2013 pooled analysis, which assembled a larger dataset than all other attempts to assess dose-response combined. Clearly, earlier reviews could not have integrated the results from these recent studies. Based upon the above results, in my opinion there is evidence of a dose-response relationship.

It is of interest that an IARC Advisory Group recommended in 2019 that IARC should give high priority to undertake a new evaluation of talc carcinogenicity. (IARC Advisory Group 2019) This implies, as I discussed above, that there has indeed been meaningful new information published on talc carcinogenicity since the 2006 IARC evaluation.

12. RECENT REVIEWS AND OPINIONS

Up to the mid 2010s most of the publications concerning talc and cancer were reports of individual epidemiologic studies. As indicated in this report there have been around 30 to 40 distinct papers describing original results concerning use of cosmetic talc and risk of ovarian cancer, in specific populations using specific methods. While there were a few attempts to synthesize the evidence with meta-analyses or review articles going back to the early 2000's (the most authoritative one being the IARC Monograph #93), there were not many of those until about the mid-2010's. About 10 years ago, the topic became more controversial and several authors have tried to synthesize evidence with meta-analyses or review articles. In the previous chapter I reviewed the meta-analyses conducted since 2017. In this chapter I review some of the recent review articles and reports, notably the following: Goodman 2020; Wentzensen 2021; Micha 2022; Tran 2022; Lynch 2023; Health Canada 2021. Some of these reviews focused solely on the epidemiologic evidence, while some also considered toxicologic and mechanistic evidence.

Goodman 2020 is a comprehensive review of evidence including epidemiologic studies, animal experimentation and some mechanistic evidence. It was carried out by a private research firm. Their conclusion was that the totality of evidence demonstrates the "non-carcinogenicity" of perineal use of talc.

While they have cited and mentioned many of the epidemiologic studies that were cited in the four meta-analyses I have mentioned above and in my Table 4, there are several serious methodological flaws with their evaluation of the epidemiologic evidence.

First, it is curious that they did not conduct a meta-analysis to estimate the RR from the ensemble of epidemiologic studies. They have all the material needed to do so. Instead they rely on a fatally flawed method of using statistical significance of individual studies and tallying up how many studies are individually statistically significant to guide their overall conclusion. The most elementary awareness of the meaning of statistical significance would contra-indicate such an inferential path. Indeed the methods of meta-analysis were developed precisely to avoid making such flawed inferences.

Second, they make the basic error of asserting that cohort studies are across the board superior in validity than case-control studies. I have addressed this error in section 9 on misinterpretations and misconceptions.

Third some of the papers they list are in fact subsumed by other papers in their list because they represent earlier analyses of the same study, or they represent different configurations of the same study.

Fourth, their interpretation of the conformity of the studies with Bradford Hill's "considerations" is subjective and unreliable.

Fifth, while they point out many gaps in knowledge regarding transport of fibers and mechanisms of carcinogenesis, they tend to interpret the absence of evidence as evidence against an association.

Taken together, these flaws invalidate the authors' conclusions.

Lynch 2023. This paper is reminiscent of the Goodman 2020 review. It has similar methods and similar flaws. It is a wide-rangeing attempt to present epidemiologic and experimental and physiological data to refute the evidence of a causal relationship between perineal talc powder and ovarian cancer. Like Goodman 2020, they refrain from conducting or referring to a meta-analysis of the data, even to the meta-analysis that members of this team published a few years ago (Berge 2018). Like Goodman 2020, they rely on the statistical significance of the results of individual studies to guide overall inferences. These tactics are flawed here as they are in Goodman 2020. They devised a so-called quality score for each study that allowed them to disregard from consideration any studies they deemed sub-par. Having gone to that trouble, they did not even conduct a meta-analysis with the papers that survived their subjective "quality cull". They assert that there were no dose-response patterns, whereas the evidence presented in my section 8.3 (and Tables 6-8 and papers by Terry 2013 and Woolen 2022) demonstrate that when sufficient data are assembled, the dose-response patterns which are hard to discern with sparse data, appear quite readily. In reviewing other domains of evidence, they indicate that the evidence regarding migration and translocation of talc particles is inconclusive, and that evidence regarding potential mechanisms of talc carcinogenesis is sparse. Like the Goodman 2020 paper, Lynch 2023 suffers from serious flaws, not least from

unjustified conclusions. The thrust of their discussion of the evidence, as they see it, is that the various dimensions of evidence are inconconclusive. When it comes time at the end to crystalize all of this uncertainty into a conclusion, they conclude with a rather assertive certainty that there is "suggestive evidence of no association for exposure to talc and ovarian cancer".

Wentzensen 2021. This rather short paper provides a balanced and thoughtful review of many aspects of the evidence. They debunk the notion, expressed by Goodman 2020 , Lynch 2023, and others, that cohort studies as a class are more valid than case-control studies. They describe various types of bias that can infect these studies, and that can distort the associations in various directions. They considered the results of the various meta-analyses that I referenced in Table 4 (except my meta-analysis, which was not published). They asserted the importance of distinguishing risk analyses among women who had intact reproductive systems, and they noted that the few studies that had data on this tended to show that women with intact reproductive systems and used talc powder had particularly high risks of ovarian cancer. They note the importance of examining results according to subtypes of ovarian cancer, but also acknowledge that there is not a lot of definitive data in this regard.

They indicate that talc causes inflammatory reactions. They acknowledge that there is convincing evidence of an association between talc exposure and ovarian cancer, but they highlight gaps in scientific knowledge that, in their opinion, preclude a definitive determination of causality.

Micha 2022 is a very brief and synthetic commentary on the nature of evidence for a talc and ovarian cancer association. It isquite superficial and does not get "into the weeds" of the studies and data on the issue. The paper focuses on the issue of asbestos content in talc. The authors tend to dismiss the possibility of a causal association between talc and ovarian cancer.

Tran 2022 is a rejoinder to Micha 2022. It is focused on the possible role of asbestos both as a component of talc powder and as an example of the possible transport of fibers to the ovaries. Contradicting Micha 2022, the authors of Tran 2022 insist that talc powder which contained asbestos could indeed be the responsible agent in causing ovarian cancers.

Health Canada 2021, referenced as ECCC & HC 2021. While many agencies and organizations and institutions publish information on recognized carcinogens, for the most part these agencies and organizations and institutions do not carry out systematic expert reviews of the basic data needed to evaluate carcinogenicity. Rather, they mostly consult publications from the few agencies that do carry out such evaluations, or they rely on subjective opinions of scientists who try to ascertain what is the accumulated wisdom on the topic. The IARC Monograph program is one of the rare agencies that routinely produces evaluations of carcinogenicity on the basis of rigorous comprehensive time-intensive evaluations by multidisciplinary groups of scientists. Some other agencies have carried out, on an ad hoc basis, some assessments of talc carcinogenicity that are at a high level of scientific investment and credibility. The Canadian federal departments of Health and of Environment teamed up to conduct a multidisciplinary evaluation of the impact of talc on the environment and on human health. Following a lengthy period of reviewing a great deal of evidence, they recently published a publicly-available report.[4]

This comprehensive systematic review of all facets of impact of talc on the environment and on human health involved government scientists and scientists from outside government. Among the potential impacts considered was that of ovarian cancer as a result of perineal exposure.

The Health Canada report considers that the presence or absence of asbestos in historic talc products remains an unsettled topic, and they decided to conduct the evaluation of talc without factoring in the possibility of asbestos being part of the exposure materials. Reflecting the expertise of the scientists who conducted the assessment, the report has a decidedly toxicology flavor. Concerning environmental impact, the report concludes that there is no evidence of harm to the environment from talc. Concerning human health impact, the report concludes that there is plausible evidence that talc particles "may transfer from the vagina to the fallopian tubes and ovaries following perineal application". Based on their expert analysis of the toxicology database, the report affirms that "Recent research with respect to specific mechanisms (inflammation and/or tumour precursor

[4] For the sake of transparency, I mention that I submitted an opinion to Health Canada on the topic of talc carcinogenicity following a public solicitation of opinions by Health Canada.

events) add increased support to the biological plausibility." The report concludes that, notwithstanding the fact that there remain gaps and uncertainties in the evidence, the review of the totality of evidence is "indicative of a causal effect" between talc powdering and ovarian cancer. The Executive Summary states: "*With regards to perineal exposure, analyses of the available human studies in the peer-reviewed literature indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer. The available data are indicative of a causal effect.*"

13. CONCLUSION

The totality of evidence demonstrates that perineal or genital use of talcum powder products is associated with ovarian cancer. Based on contemporary data, my estimated RR between ever perineal use of talc powder products and ovarian cancer is 1.30 (95%CI 1.21-1.40). The body of epidemiologic evidence is remarkably consistent in demonstrating an excess risk. The evidence summarized in Table 6 is compatible with the presence of a dose-response relationship between cumulative exposure to talcum powder products and ovarian cancer. There are various potential sources of bias in these studies, some of which could have inflated the true RR estimate and some of which would have deflated the true RR estimate. Apart from random measurement error, which is inevitable in such studies and which tends to attenuate the RR estimates, there is no certainty that the other potential biases were in fact operative and to what degree. It is my opinion, however, that neither bias nor confounding explains the consistent positive association seen across studies. Additionally, there are biologically plausible mechanisms by which talcum powder products could cause ovarian cancer.

Based on the totality of the evidence, it is my opinion, to a reasonable degree of scientific certainty, that the perineal use of talcum powder products can cause ovarian cancer. Given the seriousness of ovarian cancer and its associated morbidity, this causal association represents an important public health issue.

14. TABLES

TABLE 1. COMPONENT ACTIVITIES IN MY EVALUATION OF GENERAL CAUSATION BETWEEN TALCUM POWDER PRODUCT USE AND OVARIAN CANCER

1. Identify all epidemiology study papers that present original results on talc and Ovarian Cancer.
2. Extract all RR results from every paper into a database.
3. Determine which of the papers and results present truly independent and relevant results.
4. Extract from each study the RR for Ever/Never use of talc in the genital area in relation to OC risk.
5. Conduct a Meta-analysis.
6. Consider other meta-analyses that have been published on this topic.
6. Examine the evidence about a possible dose-response relationship.
7. Consider issues of bias, confounding and other sources of error in the various studies.
8. Consider relevant opinion pieces, review articles, and agency reports.
9. Consider opinions from experts regarding possible biological mechanisms.
10. Consider all relevant aspects of the association to infer causation.
11. Write report.

TABLE 2. RELATIVE RISK ESTIMATES BETWEEN EVER REGULAR USE OF TALCUM POWDERS PRODUCTS[1] IN THE PERINEAL AREA AND OVARIAN CANCER[2], FROM VARIOUS PUBLICATIONS USED IN ANY OF THE META-ANALYSIS, EITHER DIRECTLY OR BY CONTRIBUTING TO ANOTHER PUBLICATION THAT WAS USED IN THE META-ANALYSES

		All ovarian cancers		
Author[3]	**Included in Main meta-analysis**	**Number exposed cases**	**RR[4]**	**95% CI[5]**
Booth 1989	√	141	1.29	0.92 - 1.80
Chen, 1992	√	7	3.9	0.91 - 10.6
Cook 1997	√	159	1.5	1.1 - 2.0
Cramer 1982	√	60	1.55	0.98 - 2.47
Cramer 2016		642	1.33	1.16 - 1.52
Gates 2010		231[6]	1.06	0.89 - 1.28
Godard 1998	√	18	2.49	0.94 - 6.58
Gonzalez 2016		17	0.73	0.44 - 1.2
Harlow 1989	√	49	1.1	0.7 - 2.1
Harlow 1992	√	114	1.5	1.0 - 2.1
Hartge 1983	√	7	2.5	0.7 - 10.0
Houghton 2014		181	1.12	0.92 - 1.36

Author[3]	Included in Main meta-analysis	All ovarian cancers		
		Number exposed cases	RR[4]	95% CI[5]
Mills 2004	√	106	1.37	1.02 - 1.85
Ness 2000	√	161	1.5	1.1 - 2.0
O'Brien 2020 A[7]	√	623	1.13	1.01 - 1.26
O'Brien 2020 B[7]		954	1.08	0.99 - 1.17
Purdie 1995	√	467	1.27	1.04 - 1.54
Rosenblatt 1992	√	22	1.7	0.7 - 3.9
Schildkraut 2016 A[8]	√	248	1.44	1.11 - 1.86
Schildkraut 2016 B[8]		128	1.19	0.87 - 1.63
Shushan 1996		21	1.97	1.06 - 3.66
Terry 2013	√	2600	1.24	1.15 - 1.33
Terry-AUS 2013		705	1.13	0.92 - 1.38
Terry-DOV 2013		272	1.13	0.93 - 1.36
Terry-HAW 2013		74	0.99	0.70 - 1.41
Terry-HOP 2013		194	1.34	1.07 - 1.67
Terry-NCO 2013		195	1.37	1.05 - 1.80

Author[3]	Included in Main meta-analysis	All ovarian cancers		
		Number exposed cases	RR[4]	95% CI[5]
Terry-NEC 2013		755	1.28	1.12 - 1.47
Terry-SON 2013		197	1.35	1.03 - 1.76
Terry-USC 2013		208	1.36	1.06 - 1.74
Tzonou 1993	√	6	1.05	0.28 - 3.98
Whittemore 1988	√	67	1.36	0.91 - 2.04
Wong 1999	√	157	1.0	0.8 - 1.3
Wu 2015[9]	√	701	1.46	1.27 - 1.69

1. In all of these studies the exposure was defined as ever use of powder in the perineal area. In most studies it was further explicitly indicated that the use was regular.
2. In this table we report the result for all types of ovarian cancer combined. With the exception of the Harlow 1989 study that was restricted to borderline tumours, we have assumed that all studies included both borderline and invasive tumours, although this was not always clear in the publications.
3. See Appendix A for a list of additional publications that were excluded from meta-analyses and the reasons for those exclusions.
4. RR or OR.
5. The confidence intervals are the ones reported by the authors of the respective studies. However in its implementation procedures, the Comprehensive Meta-analysis package recomputes them to be symmetric around the point estimate, on a log scale. Consequently, in the printout of the forest plot of meta-analyses, the printed confidence interval is not always identical to the one shown in this table.
6. Estimated based on Table 1 of Gates 2010.
7. The O'Brien 2020 pooled cohort studies paper presented two sets of results that both have some legitimacy for the present purpose. O'Brien 2020A shows results for all subjects who had a patent reproductive tract; O'Brien 2020B shows results for all subjects including those who did not have a patent reproductive tract. In theory women without a patent reproductive tract would not be eligible for talc particles deposited in the vagina to migrate to the ovaries, and therefore this group were not at risk and should be

excluded. However there are about 20 other studies in the meta-analysis and it is not clear if they were able to exclude women without patent reproductive tracts. The numbers of exposed cases in the O'Brien 2020 paper were computed from data shown in the paper as follows. The paper shows the number of cases (A: 1384; B: 2168). It also shows in each group the prevalence of powder use among cases (A45%; B: 44%). The numbers of exposed cases is the product of those two parameters (A: 0.45 x 1384; B: 0.44 x 2168).

8. The Schildkraut 2016 case-control study presented two sets of results that both have some legitimacy for the present purpose. Schildkraut 2016A shows the results for all subjects who were interviewed in the study from 2010-2015. Schildkraut2016B shows the results for those subjects who were interviewed before 2014, and who, according to the authors, were not susceptible to having been tainted by publicity from a class action suit.

9. The Wu 2015 paper is from the same study that gave rise to the Terry-USC component of the Terry 2013 paper. By including both the Terry 2013 paper and the Wu 2015 papers in my main meta-analysis, this compromises the principle of not double-counting some cases. The alternative would be to include Terry 2013 and exclude Wu 2015. But as can be seen from the numbers of exposed cases in Wu 2015 and Terry-USC 2013, there and many more cases, and therefore useful information, in the Wu 2015 estimate of RR than in the Terry-USC 2013 estimate of RR (701 exposed cases vs 208 exposed cases). Consequently, without being able to separate out the USC-Wu study subjects who were part of the Terry analysis from those who were part of the Wu 2015 analysis, the strategy adopted here is the most efficient.

TABLE 3. MAIN META-ANALYSIS AND SENSITIVITY ANALYSES CONDUCTED ON THE ASSOCIATION BETWEEN EVER REGULAR USE OF TALCUM POWDER PRODUCTS IN THE PERINEAL AREA AND OVARIAN CANCER (ALL TYPES COMBINED).

		RR estimate			Heterogeneity	
Studies in meta-analysis	**N[1]**	**Meta-RR**	**95% CI**	**p-value**	**I^2(%)**	**p-value**
1. Main Meta-Analysis studies as per Table 2	19	1.30	1.21 - 1.40	0.00	25.2	0.15
Sensitivity analyses (modification to Main meta-analysis I)						
II. Substitute O'Brien B for O'Brien A	19	1.30	1.20 - 1.42	0.00	45.0	0.02
III. Substitute Schildkraut B for Schildkraut A.	19	1.29	1.20 - 1.38	0.00	22.5	0.18
IV. Add Shushan	20	1.31	1.22 - 1.41	0.00	26.9	0.13
V. Drop Terry 2013 and O'Brien 2020. Add all constituent studies from Terry 2013 and O'Brien 2020[2].	29	1.26	1.19 - 1.33	0.00	21.9	0.15

1. N: Number of RRs that went into the meta-analysis. This is not synonymous with the number of studies because some RRs (e.g. Terry 2013, Cramer 2016, O'Brien 2020) embody multiple studies.

2. Sources of data on constituent studies:
For case-control studies in Terry 2013: Cramer 2016; Wu 2015; Terry-Aus 2013; Terry-DOV 2013; Terry-Haw 2013; Terry-HOP 2013; Terry-NCO 2013; Terry SON 2013.
For cohort studies in O'Brien 2020: O'Brien 2020.

TABLE 4. COMPARISON OF RESULTS OF FOUR RECENT AND INDEPENDENT META-ANALYSES OF THE ASSOCIATION BETWEEN EVER REGULAR USE OF TALCUM POWDER PRODUCTS IN THE PERINEAL AREA AND OVARIAN CANCER.

Meta-analysis author	N[1]	Meta-RR	95% CI	Heterogeneity p-value
Siemiatycki 2020	19	1.30	1.21 - 1.40	0.15
Taher 2019	27	1.28	1.20 - 1.37	0.00
Penninkilampi 2018	26	1.35	1.24 - 1.39	0.31
Berge 2018	27	1.22	1.13 - 1.30	0.02

1. Number of published RR estimates that went into the meta-analysis. This does not necessarily correspond to the number of studies, since, for example, the Terry 2013 pooled estimate used in the Siemiatycki meta-analysis embodied 10 studies and the O'Brien 2020 pooled estimate used in the Siemiatycki meta-analysis embodied 4 studies.

TABLE 5. RELATIVE RISK ESTIMATES BETWEEN EVER REGULAR USE OF TALCUM POWDER PRODUCTS ON SANITARY NAPKINS AND OVARIAN CANCER, AND RESULTS OF META-ANALYSIS.

Author	Number exposed cases	RR[1]	95% CI[2]
Chang 1997	51	1.26	0.81 - 1.96
Cook 1997	38	0.9	0.5 - 1.5
Cramer 1999	20	1.45	0.68 - 3.09
Gertig 2000	32	0.89	0.61 - 1.28
Harlow 1989	8	2.6	0.9 - 22.4[2]
Harlow 1992	9	1.1	0.4 - 2.8
Houghton 2014	93	0.95	0.76 - 1.20
Ness 2000	77	1.6	1.1 - 2.3
Rosenblatt 1992	21	4.8	1.3 - 17.8
Rosenblatt 2011	55	0.82	0.58 - 1.16
Whittemore 1988	5	0.62	0.21 - 1.80
Wong 1999	13	0.9	0.4 - 2.0
Meta-analysis		**1.08**	**0.89 - 1.31**
		p-value for heterogeneity = 0.09	

1. RR or OR.
2. The confidence intervals are the ones reported by the authors of the respective studies. However in its implementation procedures, the Comprehensive Meta-analysis package recomputes them to be symmetric around the point estimate, on a log scale. Consequently, in the printout of the forest plot of meta-analyses, the printed confidence interval is not always identical to the one shown in this table.

3. These studies were excluded from the Ever/Never exposed analyses in Table 2 because they were superseded by subsequent pooled analyses (Terry 2013 or O'Brien 2020). However those pooled analyses did not report on risks related to powdering on sanitary napkins, so we reverted to the available results from these component studies.

TABLE 6. RELATIVE RISK ESTIMATES BETWEEN SUBGROUPS DEFINED BY CUMULATIVE EXPOSURE MEASURES[1] AND OVARIAN CANCER[2], FROM VARIOUS STUDIES.

Author	Cumulative applications[3]	Number exposed cases	RR[4]	95% CI
Cook 1997[4]	< 2000	20	1.8	0.9 - 3.5
	2001-5000	24	1.6	0.9 - 2.9
	5001-10000	21	1.2	0.6 - 2.4
	>10000	*28*	*1.8*	*0.9 - 3.4*
Harlow 1992	<1000	18	1.3	0.7 - 2.7
	1000-10000	54	1.5	0.9 - 2.4
	>10000	*42*	*1.8*	*1.0 - 3.0*
Mills 2004	Quartile 1	18	1.0	0.6 - 1.8
	Quartile 2	28	1.8	1.1 - 3.0
	Quartile 3	34	1.7	1.1 - 2.7
	Quartile 4	*20*	*1.1*	*0.6 - 1.8*
Schildkraut 2016	≤3600	92	1.16	0.83 - 1.63
	>3600	*152*	*1.67*	*1.23 - 2.26*
Terry 2013[5]	Quartile 1	534	1.14	1.00 - 1.31
	Quartile 2	541	1.23	1.08 - 1.41
	Quartile 3	542	1.22	1.07 - 1.40
	Quartile 4	*586*	*1.32*	*1.16 - 1.52*
Meta RR for highest category of each study as reported by authors			***1.39***	***1.23 - 1.57***

1. These were all studies that collected information on perineal use of hygiene powders in such a way as to allow construction of a cumulative measure. All of these were case control studies.
2. In this table we report the result for all types of ovarian cancer combined, as reported by the authors.
3. For the Cook study the metric was the number of days on which the woman had ever applied the powder. For the other studies the metric is based on an estimate of the total number of applications.
4. RR or OR.
5. This study was based on a pooling of studies from 8 teams. Two of the teams (Cramer 2016 and Rosenblatt 2011) published separate analyses of risk by cumulative number of applications. But these are not shown here because they are rendered redundant by the Terry 2013 pooled results.
6. We used the RR result in the highest category as listed above in italics.

TABLE 7. RELATIVE RISK ESTIMATES BETWEEN SUBGROUPS DEFINED BY DURATION OF USE[1] AND OVARIAN CANCER[2], FROM VARIOUS STUDIES.

Author	Duration of use	Number exposed cases	RR[4]	95% CI
Chang 1997	<30	60	1.7	1.1 - 2.6
	30-40	71	1.4	1.0 - 2.2
	>40	*41*	*0.9*	*0.5 - 1.4*
Cramer 1999	<20 years	55	1.9	1.2 - 3.0
	20-30 years	32	1.3	0.8 - 2.3
	>30 years	*59*	*1.4*	*0.9 - 2.3*
Cramer 2016	< 8 years of use	133	1.31	1.03 - 1.68
	8-19 years of use	126	1.31	1.02 - 1.68
	20-35 years of use	147	1.35	1.07 - 1.70
	>35 years of use	*129*	*1.33*	*1.03 - 1.71*
Harlow 1992	<10 years	14	1.2	0.5 - 2.6
	10-29 years	49	1.6	1.0 - 2.7
	> 30 years	*51*	*1.6*	*1.0 - 2.7*
Ness 2000	<1 year	17	2.0	1.0 - 4.0
	1-4 years	76	1.6	1.1 - 2.3
	5-9 years	40	1.1	0.8 - 1.9
	>10 years	*233*	*1.2*	*1.0 - 1.5*
Mills 2004	<3 years	18	1.0	0.6 - 1.8
	4-12 years	32	1.9	1.2 - 3.0
	13-30 years	29	1.5	0.9 - 2.3
	>30 years	*21*	*1.2*	*0.7 - 2.1*
O'Brien 2020	*"Long-term"*	*64[5]*	*1.00*	*0.76 - 1.32*

Rosenblatt 2011	1-9 years	33	1.39	0.85 - 2.28
	10-19 years	29	1.46	0.87 - 2.45
	20-34 years	30	1.28	0.78 - 2.10
	35+ years	*19*	*0.91*	*0.51 - 1.62*
Schildkraut 2016	≤20 years	101	1.33	0.95 - 1.86
	>20 years	*144*	*1.52*	*1.11 - 2.07*
Whittemore 1988	1-9 years	34	1.6	1.0 - 2.6
	10+	*50*	*1.1*	*0.7 - 1.7*
Wong 1999	1-9 years	39	0.9	0.6 - 1.5
	10-19 years	49	1.4	0.9 - 2.2
	>20 years	*101*	*0.9*	*0.6 - 1.2*
Wu 2015	Per 5 years of exposure	1273	1.14	1.09 - 1.20
Meta-RR for highest category of each study as reported by authors[6]			**1.24**	**1.07 - 1.45**

1. These were all studies that collected information on perineal use of hygiene powders in such a way as to allow construction of a measure of duration.
2. In this table we report the result for all types of ovarian cancer combined, as reported by the authors.
3. Years of case ascertainment or follow-up: For case-control studies this indicates the years in which cases were ascertained and data collected; for cohort studies it indicates the years of enrolment and follow-up.
4. RR or OR.
5. See Table 2, footnote 6.
6. We used the RR result in the highest category as listed above in italics. For the Wu 2015 study, we estimated the RR corresponding to 25 years exposure, by multiplying the log of the 5-year estimate by 5 and recomputing the anti-log.

TABLE 8. RELATIVE RISK ESTIMATES BETWEEN SUBGROUPS DEFINED BY MEASURES OF FREQUENCY OF USE[1] AND OVARIAN CANCER[2], FROM VARIOUS STUDIES.

Author	Frequency of use	Number exposed cases	RR[4]	95% CI
Booth 1989	Rarely	6	0.9	0.3 - 2.4
	Monthly	7	0.7	0.3 - 1.8
	Weekly	57	2.0	1.3 - 3.4
	Daily	*71*	*1.3*	*0.8 - 1.9*
Chang 1997	<10 per month	76	1.8	1.2 - 2.7
	10-25 per month	*54*	*1.1*	*0.7 - 1.7*
Cramer 1999	<30 per month	64	2.2	1.4 - 3.6
	30-39 per month	59	1.7	0.8 - 1.8
	≥40 per month	*23*	*1.7*	*0.8 - 3.1*
Cramer 2016	1-7 days per month	220	1.17	0.96 - 1.44
	8-29 days per month	110	1.37	1.05 - 1.78
	>30 days per month	*205*	*1.46*	*1.20 - 1.78*
Harlow 1992	<5 per month	32	1.5	0.8 - 2.7
	5-29 per month	24	1.2	0.6 - 2.2
	≥30 per month	*58*	*1.8*	*1.1 - 3.0*
Mills 2004	<1 per week	34	1.3	0.9 - 2.1
	1-3 per week	31	1.6	0.7 - 1.8
	4-7 per week	*41*	*1.7*	*1.1 - 2.6*
O'Brien	*>1 / week*	*285[5]*	*1.19*	*1.03 - 1.37*

Author	Frequency of use	Number exposed cases	RR[4]	95% CI
Schildkraut 2016	<Daily	88	1.12	0.80 - 1.58
	Daily	*158*	*1.71*	*1.26 - 2.33*
Whittemore 1988	1-20 per month	41	1.3	0.8 - 2.0
	>20 per month	*44*	*1.5*	*0.9 - 2.2*
Meta-RR for highest category of each study as reported by authors[6]			***1.39***	***1.24 - 1.56***

1. These were all studies that collected information on perineal use of hygiene powders in such a way as to allow construction of a measure of frequency of use.
2. In this table we report the result for all types of ovarian cancer combined, as reported by the authors.
3. Years of case ascertainment or follow-up: For case-control studies this indicates the years in which cases were ascertained and data collected; for cohort studies it indicates the years of enrolment and follow-up.
4. RR or OR
5. See Table 2, footnote 6.
6. We used the RR result in the highest category as listed above in italics.

TABLE 9. RELATIVE RISK ESTIMATES BETWEEN EVER REGULAR USE OF TALCUM POWDER PRODUCTS IN THE PERINEAL AREA AND CERTAIN SUBTYPES OF OVARIAN CANCER, FROM TWO POOLED ANALYSES

	Terry 2013			O'Brien 2020		
Histotype	**n[1]**	**RR**	**95% CI**	**n[2]**	**RR**	**95% CI**
Serous	1197	1.24	1.13 - 1.35	457	1.10	0.97 - 1.25
Endometroid	304	1.20	1.03 - 1.40	69	1.15	0.83 - 1.58
Mucinous	94	1.06	0.82 - 1.36	44	1.03	0.59 - 1.54
Clear cell	187	1.26	1.04 - 1.52	30	1.17	0.73 - 1.89

1. Number of exposed cases.
2. I computed these by multiplying the number of cases (Table 4) by 0.44 (from Table 2).

TABLE 10. RELATIVE RISK ESTIMATES BETWEEN EVER REGULAR USE OF TALCUM POWDER PRODUCTS[1] IN THE PERINEAL AREA AND INVASIVE SEROUS OVARIAN CANCER, FROM VARIOUS STUDIES.

Author	Number exposed cases	RR[2]	95% CI[3]
Cook 1997	71	1.7	1.1 - 2.5
Harlow 1992	60	1.4	0.9 - 2.2
Mills 2004	42	1.77	1.12 - 2.81
O'Brien 2020	457[4]	1.10	0.97 - 1.25
Schildkraut 2016	165	1.38	1.03 - 1.85
Terry 2013	1197	1.24	1.13 - 1.35
Wong 1999	136	1.2	0.7 - 2.1
Meta-analysis		**1.26**	**1.13 - 1.40**
			p-value for heterogeneity 0.19

1. In all of these studies the exposure was defined as ever use of powder in the perineal area. In most studies it was further explicitly indicated that the use was regular.
2. RR or OR.
3. The confidence intervals are the ones reported by the authors of the respective studies. However in its implementation procedures, the Comprehensive Meta-analysis package recomputes them to be symmetric around the point estimate, on a log scale. Consequently, in the printout of the forest plot of meta-analyses, the printed confidence interval is not always identical to the one shown in this table.
4. The paper does not show this number. I computed it as 0.44 (from Table 2) x 1038 (from Table 4).

TABLE 11. SOME MAJOR MISCONCEPTIONS IN REVIEWING EVIDENCE ON TALC AND OVARIAN CANCER

1. Cohort studies are more valid and informative than case-control studies.
2. Hospital-based case-control studies are more valid and informative than the population-based case-control studies.
3. Counting the number of "statistically significant" results is a valid way of assessing the consistency of results among multiple studies.
4. If a product has been used for a long time, it must be safe
5. You cannot prove causality with an RR less than 2.0.
6. Government agencies provide a reliable up-to-date source of scientific information.
7. A biological mechanism must be proven before we can establish causality
8. Bradford-Hill "aspects" represent a recipe list of necessary ingredients.

TABLE 12. SELECTED EXAMPLES OF SOME OF THE RECOGNIZED CAUSAL ASSOCIATIONS THAT HAVE RR LESS THAN 2.0

Agent	Disease	Approximate RR
Urban air pollution	Lung cancer	1.09[1]
Trichloroethylene	Kidney cancer	1.32[2]
Diesel engine emissions	Lung cancer	1.42[3]
Benzene	Leukemia	1.72[4]
Domestic radon gas	Lung cancer	1.29[5]
Second hand cigarette smoke	Lung cancer	1.64[6]
Intermittent intense sun exposure	Melanoma of the skin	1.61[7]
Estrogen-progestin menopausal therapy	Breast cancer	1.59[8]
Cigarette smoking	Cardiovascular disease	1.6[9]
Physically inactive (compared with physically active)	Hypertension	1.19[10]
Physically inactive (compared with physically active)	Diabetes	1.12[10]
Low fruit and vegetable diet	Cardiovascular disease	1.09[11]

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9. Doll R, Peto R, Boreham J, Sutherland I (2004). Mortality in relation to smoking: 50 years' observations on British male doctors, *British Medical Journal*, 328(7455):1519.
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11. Aune D, Giovannucci E, Boffetta P, Fadnes L, Keum N, Norat T, Greenwood D, Riboli E, Vatten L, Tonstad S (2017). Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality – a systematic review and dose-response meta-analysis of prospective studies, International Journal of Epidemiology 43(3):1029-1056. (This RR estimate is computed from the reciprocal of the High fruit and vegetable variable that was reported by the authors.: that is, 1/0.92).

TABLE 13. BRADFORD HILL ASPECTS IN RELATION TO PERINEAL TALC EXPOSURE AND OVARIAN CANCER

Aspect	Brief comment	Weight in evaluating causality
Strength of the association	Highly statistically significant RR of 1.30	High
Dose response relationship	Reasonably clear increase in risk with increasing exposure	High
Consideration of alternative explanations – absence of bias	Yes considered, and none is compelling	High
Replication of the findings	Very strong, almost all studies support association	High
Temporal relationship	Exposure preceded disease in all studies	Moderate
Biological plausibility	There are plausible mechanisms	Moderate
Specificity of the association	Yes, talc is not associated with a multitude of diseases	Less
Coherence with other knowledge	Could be similar to asbestos carcinogenicity	Less
Cessation of exposure	Not applicable.	Less
Analogy		Less

15. FIGURES

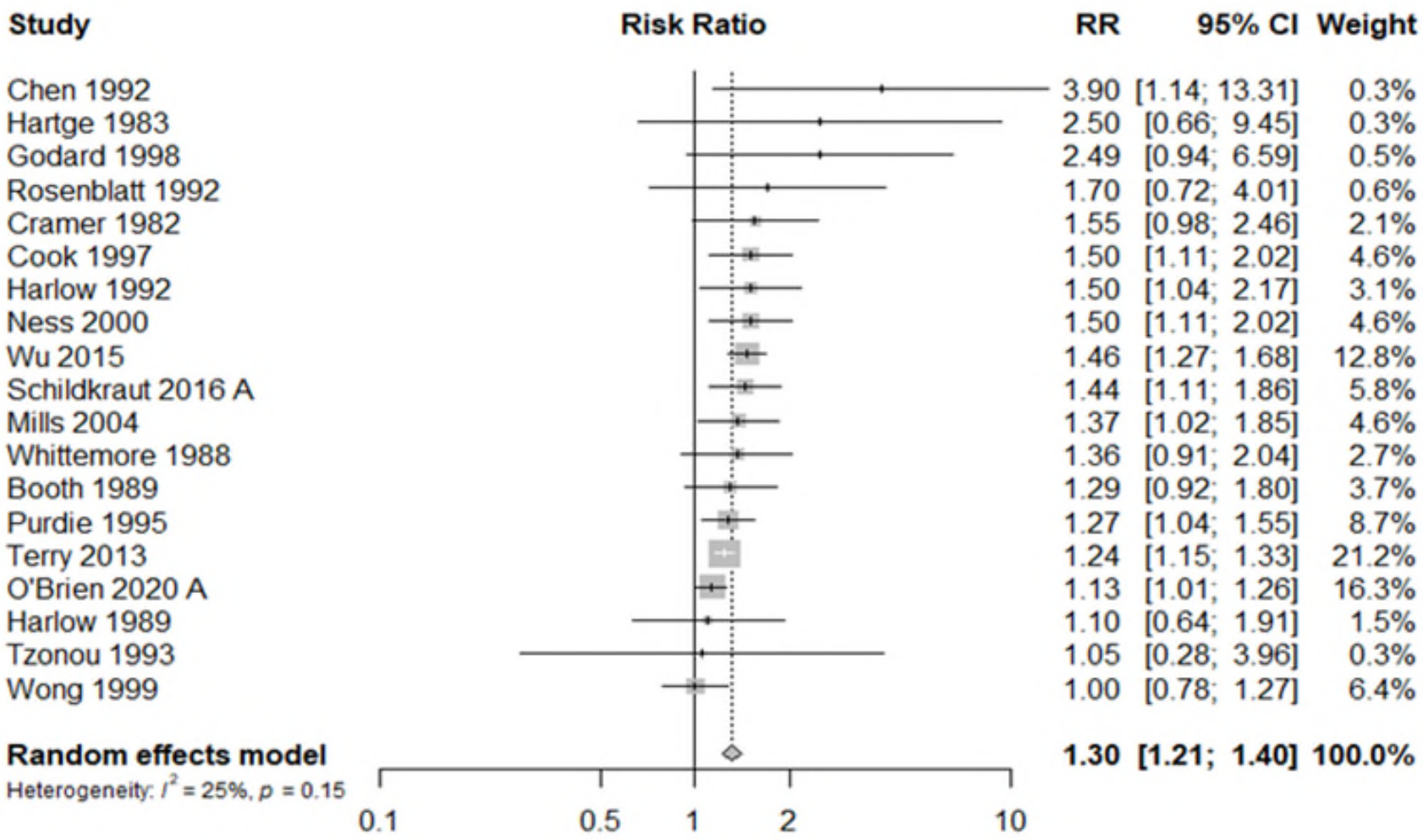

FIGURE 1. MAIN META-ANALYSIS CONDUCTED ON THE ASSOCIATION BETWEEN EVER REGULAR USE OF TALCUM POWDER PRODUCTS IN THE PERINEAL AREA AND OVARIAN CANCER (ALL TYPES COMBINED). CORRESPONDING TO TABLE 3, ANALYSIS I.

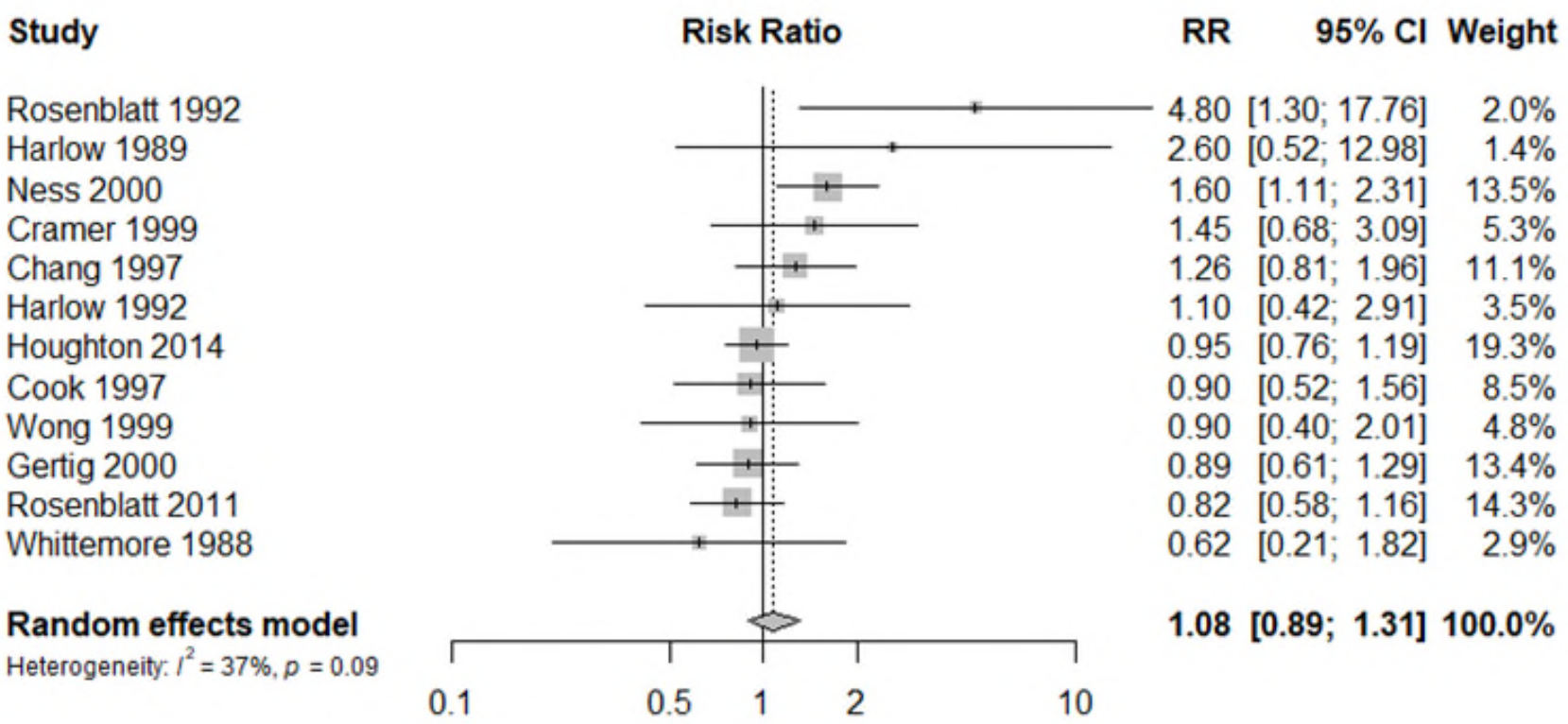

FIGURE 2. META-ANALYSIS OF RELATIVE RISK OF OVARIAN CANCER (ALL TYPES COMBINED) AMONG WOMEN WHO REGULARLY USED TALCUM POWDER PRODUCTS ON SANITARY NAPKINS, BASED ON ALL INFORMATIVE STUDIES. CORRESPONDING TO TABLE 5.

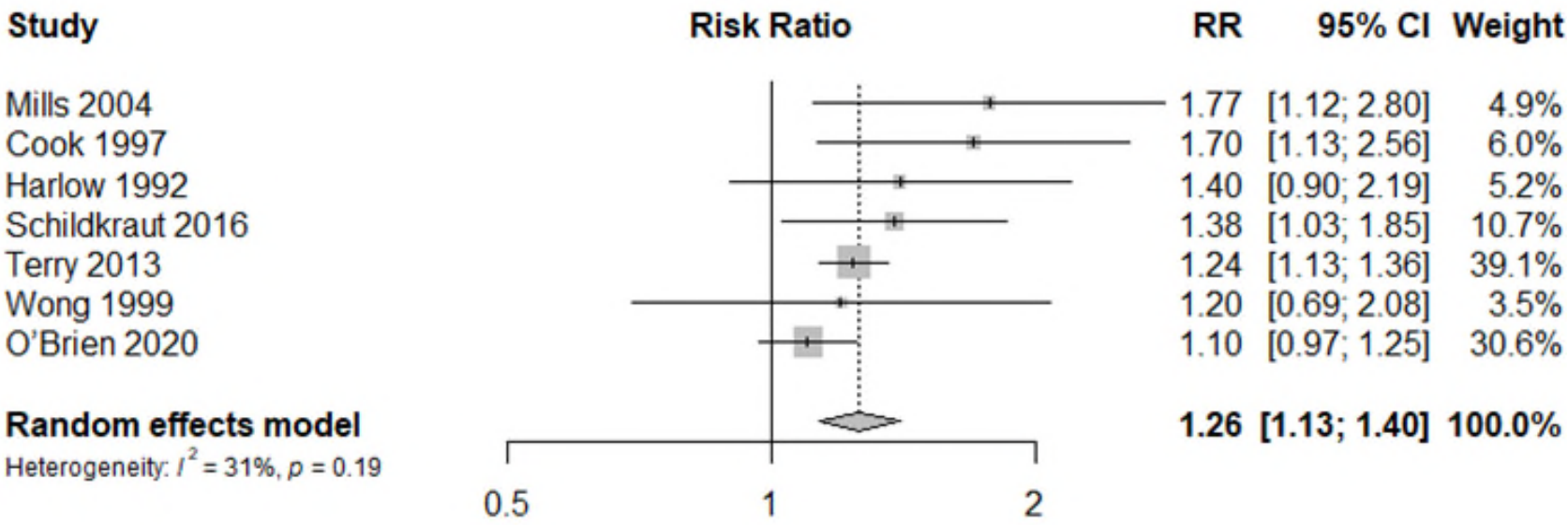

FIGURE 3. META-ANALYSIS OF RELATIVE RISK OF INVASIVE SEROUS OVARIAN CANCER AMONG WOMEN WHO REGULARLY USED TALCUM POWDER PRODUCTS IN THE PERINEAL AREA, BASED ON ALL INFORMATIVE STUDIES. CORRESPONDING TO TABLE 10.

16. APPENDICES

APPENDIX A. PAPERS THAT CONTAIN SOME RESULTS ON THE ASSOCIATION BETWEEN EXPOSURE TO PERINEAL TALC AND OVARIAN CANCER, AND WHETHER THE PAPER WAS INCLUDED IN MY META-ANALYSES OF EVER/NEVER EXPOSED VARIABLE

Author	Included/excluded	Reasons for exclusion
Booth 1989	Core Inclusion	
Chang 1997	Core Inclusion	
Chen 1992	Core Inclusion	
Cook 1997	Core Inclusion	
Cramer 1982	Core Inclusion	
Cramer 1995	Excluded	Subsumed by Terry 2013 and Cramer 2016
Cramer 1999	Excluded	Subsumed by Terry 2013 and Cramer 2016
Cramer 2005	Excluded	Subsumed by Terry 2013 and Cramer 2016
Cramer 2016	Excluded when Terry 2013 is included	Considerable overlap between this and the Terry 2013 NEC component
Eltabbakh 1998	Excluded	Cases were peritoneal cancer and controls were ovarian cancer
Gates 2010[2]	Excluded	Subsumed by O'Brien 2020
Gertig 2000	Excluded	Subsumed by O'Brien 2020
Godard 1998	Core inclusion	

Author	Included/excluded	Reasons for exclusion
Gonzalez 2016	Excluded	Subsumed by O'Brien 2020
Green 1997	Excluded	This appears to be an analysis of a subset of the subjects in Purdie 1995
Hankinson 1993	Excluded	Numerical results were not presented
Harlow 1989	Core inclusion	
Harlow 1992	Core inclusion	
Hartge 1983	Core inclusion	
Houghton 2014	Excluded	Subsumed by O'Brien 2020
Jordan 2007	Excluded	Benign tumours only
Kurta 2012	Excluded	Subsumed by Terry 2013
Langseth 2004	Excluded	Not based on perineal application of cosmetic powder
Lo-Ciganic 2012	Excluded	Same study as Kurta 2012 and subsumed by Terry 2013
Merrit 2008	Excluded	Subsumed by Terry 2013
Mills 2004	Core inclusion	
Moorman 2009	Excluded	Subsumed by Terry 2013
Ness 2000	Core inclusion	

Author	Included/excluded	Reasons for exclusion
O'Brien 2020	Core inclusion	
Pike 2004	Excluded	Subsumed by Terry 2013
Purdie 1995	Core inclusion	
Rosenblatt 1992	Core inclusion	
Rosenblatt 2011	Core inclusion	
Schildkraut 2016	Core inclusion	
Shushan 1996	Included in one sensitivity analysis	Unclear on how they obtained data on talc exposure or what the route of exposure was
Terry 2013	Included in Main analysis, but replaced by component studies in one sensitivity analysis	
Tzonou 1983	Core inclusion	
Whittemore 1988	Core inclusion	
Wong 1999	Core inclusion	
Wu 2015	Core inclusion	

APPENDIX B1. INFORMATION ON THE STUDIES USED IN MY ANALYSES - ADMINISTRATIVE AND CONTEXTUAL ASPECTS

Author	Study location	Years of case ascertainment/ follow-up[1]	Type of study
Booth 1989	London, Oxford UK	1978-1983	Case-control; Hospital controls
Chen 1992	Beijing Cancer Registry	1984-1986	Case-control; Population controls
Cook 1997	Washington State	1986-1988	Case-control; Population controls
Cramer 1982	Boston	1978-1981	Case-control; Population controls
Cramer 2016	New England	1992-2008	Case-control; Population controls
Gates 2010[2]	USA – pooled 2 cohorts of nurses NHS and NHSII	1976-2004 1989-2005	Cohort (US Nurses)
Godard 1998	Montreal, Canada	1995-1996	Case-control; Population controls
Gonzalez 2016	Puerto Rico and 11 States USA	2003-2014	Cohort
Harlow 1989	Washington State	1980-1985	Case-control; Population controls
Harlow 1992	Boston	1984-1987	Case-control; Population controls

Author	Study location	Years of case ascertainment/ follow-up[1]	Type of study
Hartge 1983	Washington, DC	1974-77	Case-control; Population controls
Houghton 2014	USA	1993-2012	Cohort (WHI)
Mills 2004	California	2000-2001	Case-control; Population controls
Ness 2000	Pennsylvania, New Jersey, Delaware	1994-1998	Case-control; Population controls
O'Brien 2020	USA	1982-2017	Pooling of 4 cohort studies
Purdie 1995	Australia	1990-1993	Case-control; Population controls
Rosenblatt 1992	Baltimore	1981-1985	Case-control; Hospital controls
Schildkraut 2016	USA	2010-2015	Case-control; Population controls
Shushan 1996	Israel	1990-1993	Case-control Population controls
Terry 2013	USA (7 centers) & Australia (1 center)	1984-2008	Pooling of 8 Case-control studies; Population controls
Tzonou 1983	Athens	1989-1991	Case-control; Controls – hospital visitors
Whittemore 1988	San Francisco	1983-1985	Case-control; Hospital & population controls
Wong 1999	Buffalo	1982-1992	Case-control; Hospital controls
Wu 2015	Los Angeles County	1992-2008	Case-control; Population controls

1. For case-control studies this column indicates the years in which cases were ascertained and data collected; for cohort studies it indicates the years of enrolment and follow-up.

APPENDIX B2. INFORMATION ON THE STUDIES USED IN MY ANALYSES - EXPOSURE VARIABLE AND COVARIATES

Author	Exposure variable selected	Covariates used in analysis
Booth 1989	At least monthly use	Since the authors did not present results for "ever" exposed, I calculated the OR from crude numbers in their tables. Therefore the OR presented is a crude one. However, results presented in Table 7 adjusted for age and social class
Chen 1992	Dusting perineum or lower abdomen > 3 months	Education
Cook 1997	Lifetime perineal application	Age
Cramer 1982	Any use as dusting powder and/or on sanitary napkins	Parity; menopausal status
Cramer 2016	Any talc use	Age; study center (MA, NH); BMI; primary relative with breast or ovarian cancer; parity; OC use; tubal ligation
Gates 2010[1]	Regular genital talc use (1 per week or more)	Age; BMI; physical activity; smoking; family history of breast or ovarian ca; OC use; tubal ligation; hysterectomy; age menopause; estrogen use
Godard 1998	Ever use of talc on perineum	Age; reproductive factors; OC use; tubal ligation; alcohol use; breast and abdominal surgery
Gonzalez 2016	Talc use in the past 12 months	Race; body mass index; parity; duration of oral contraceptive use; baseline menopause status; and patency
Harlow 1989	Any genital talc use	Age; county; parity; OC use

Author	Exposure variable selected	Covariates used in analysis
Harlow 1992	Any genital talc use	Age; county; parity; marital status; education; religion; weight; use of sanitary napkins; douching
Hartge 1983	Any genital talc use	Race; age; gravidity
Houghton 2014	Combined use: longest duration of use among the applications to genitals, sanitary napkins and diaphragms	Age; race; OC use; HRT[3] use; family history of ovarian ca; age at last birth; BMI; smoking; tubal ligation; parity
Mills 2004	Ever use of talcum powder in genital area	Age; race/ethnicity; OC use; breast-feeding
Ness 2000	Genital rectal talc use	Age; parity; family history of ovarian ca;
O'Brien 2020	Ever used talc in perineal region (at baseline)	Age; race; education; BMI; parity; smoking; oral contraceptives; HRT; tubal ligation; hysterectomy; menopause status; (all at baseline)
Purdie 1995	Ever used talc in perineal region	Age; parity; duration of OC use; education; BMI; smoking; family history of ovarian ca
Rosenblatt 1992	Ever use of bath talc	Number of live births
Schildkraut 2016	Regular use of talc, cornstarch, baby or deodorising powder – at least once a month for 6 months	Age at diagnosis/interview; study site; education; tubal ligation; parity; BMI duration of OC use first degree family history of breast or ovarian cancer; and interview year
Shushan 1996	Talc use – never, seldom, moderate, a lot	Crude OR

Author	Exposure variable selected	Covariates used in analysis
Terry 2013 – all components of the pooled analysis	Genital powder use	Age; OC use; parity; BMI; tubal ligation; ethnicity; race; tubal ligation; hysterectomy; breastfeeding
Tzonou 1983	Ever use of talc in perineal region	Age; years of schooling; weight before onset of the disease; age at menarche; menopausal status and age at menopause; parity and age at first birth; tobacco smoking; coffee drinking; consumption of alcoholic beverages; hair dyeing; use of analgesics and tranquilizers/hypnotics
Whittemore 1988	Talcum powder used on any two of perineum, sanitary pads and diaphragm	Age; race; hospital; parity
Wong 1999	Ever use of talc on genital region or thighs	Age; income; education; geographic location; OC use; smoking; family history of ovarian ca; age at menarche; menopausal status; tubal ligation or hysterectomy
Wu 2015	Genital talc use >1 year	Age; race/ethnicity; interviewer; reproductive variables; sociodemographic variables; medical history; hormonal variables; BMI

1. OC: oral contraceptive
2. HRT: hormone replacement therapy
3. BMI: body mass index

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18. EXHIBIT A

EXHIBIT A

CURRICULUM VITAE

Jack Siemiatycki
August 2023

TABLE OF CONTENTS

STATISTICAL SUMMARY OF SELECTED ACCOMPLISHMENTS

Publications in peer-reviewed journals – total	278
- *Before 1990*	*42*
- *1991 – 2009*	*102*
- *Since 2010*	*134*
Book chapters, IARC Monographs	22
Other publications, reports	42
Book (authored)	1
Invited presentations	174
Conference presentations, posters, abstracts : offered and accepted	192
Grants received as P.I. (number)	36
Grants received as P.I. ($)	$16M
Grants received as co-investigator (number)	59
Grants received as co-investigator ($)	$28M
H-factor (google scholar)	76
Instances of participation on expert panels, committees, boards of directors, at invitation of governments or public health agencies or research agencies or universities	140
Grant review panels or referee for external institution or journal editorial boards	65
Honours	several

GENERAL INFORMATION

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Research Center of CHUM
850 rue St Denis, Montréal, QC, Canada H2W 1V1

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E-mail: j.siemiatycki@umontreal.ca

EDUCATION

1970	M.Sc. (mathematical statistics); McGill University
1976	Ph.D. (epidemiology and medical statistics); McGill University
1977	Post-doctoral (cancer epidemiology); International Agency for Research on Cancer, Lyon

ACADEMIC AND PROFESSIONAL APPOINTMENTS

1967-71	Research Fellow; Department of Epidemiology and Health, McGill University.
1970-72	Research Director; Pointe St. Charles Community Clinic, Montréal.
1978-2001	Assistant, then Associate (1979), then full Professor (1983): Epidemiology Research Center, INRS-Institut Armand-Frappier, Laval, Québec.
1996-1997	Visiting Scientist. International Agency for Research on Cancer, Lyon.
2001-2021	Full Professor, Université de Montréal.
2001-2015	Canada Research Chair (Tier 1), Université de Montréal.
1979-	Adjunct Professor, Dept Epidemiology, Biostatistics and Occupational Health, McGill University
2007 -	CRS-Guzzo Research Chair in Environment and Cancer.
2008-	Fellow, Canadian Academy of Health Sciences
2021-	Adjunct Professor, School of Public Health, Université de Montréal.

SIGNIFICANT INTERNAL ADMINISTRATIVE APPOINTMENTS

1982-86	Director, Affiliated research team of the Quebec Institute for Occupational Health and Safety on Occupational Cancer (Équipe associée de l'Institut de Recherche en Santé et Sécurité du Travail).
1988-91	Director, Epidemiology Research Center, Institut Armand-Frappier.
1990-98	Director, Priority research team in environmental epidemiology (Équipe prioritaire de recherche en épidémiologie environnementale). FRQS.
1998-2001	Member, Governing Council (Conseil d'administration). Institut national de la recherche scientifique, Université du Québec.
2000-2007	Coordinator. Program of Research in Environmental Epidemiology of Cancer (PREECAN), a national program funded by the National Cancer Institute of Canada.
2002-2005	Associate Director for Population Health Sciences, Research Center of the University of Montréal Hospital Center (CRCHUM).
2006-2007	Director, Epidemiology program, PhD public health, Université de Montréal.
2006-2014	Director, Axe risques à la santé (Health Risks Division). Centre de recherche du Centre hospitalier de l'Université de Montréal.

CURRENT MAJOR EXTERNAL BOARDS, SCIENTIFIC COMMITTEES (INVITED)

1. Chair of International Scientific Advisory Committee of CONSTANCES, a large prospective cohort established in France, under aegis of INSERM, Ministère de la Santé, and other agencies. Since 2011.
2. Member of the Board. Conseil d'administration. (Board of Directors). Société québécoise du cannabis. Since 2018.

PAST MAJOR EXTERNAL BOARDS, SCIENTIFIC COMMITTEES, CONSULTATIONS (INVITED)

1. Expert consultative committee to Commission de la santé et sécurité du travail du Québec on the epidemiologic function of the CSST. 1979-80.
2. President of Organizing Committee of Annual Congress of Quebec Public Health Association, Montréal. 1982.
3. Consultative committee of International Agency for Research on Cancer on feasibility of SEARCH programme. 1982.
4. Canadian representative. International Joint Commission (U.S. and Canada) Committee on the Assessment of Human Health Effects of Great Lakes Water Quality. 1982-89.
5. Task Force on Chemicals in the Environment and Human Reproduction Effects in New Brunswick. 1983-85.
6. Chairman and organizer of international workshop sponsored by International Agency for Research on Cancer, Lyon, on use of job exposure information in cancer case-control studies. 1984.
7. Quebec Government Consultative Committee on Alachlor. 1985-1986.
8. Associate member, McGill Cancer Center, McGill University. 1982-1986
9. Chairman and organizer of the International Joint Commission Workshop on the Role of Epidemiology in Assessing the Effects of Great Lakes Water Quality on Human Health, Scarborough, March 1988. 1986-88.
10. Priority Substances Advisory Panel. Panel established under terms of Canadian Environmental Protection Act by Health and Welfare Canada. 1988.
11. Working Group on Electromagnetic Fields under auspices of Health Effects Institute. 1991.
12. Consultative Committee on Environment-related Cancer Surveillance, LCDC, Health and Welfare Canada. 1993-1996.
13. Consultative Committee on an Investigation of Lung Cancer and Environmental Tobacco Smoke, Environmental Health Directorate, Health Canada. 1994-1995.
14. Working Group on Evaluation of Carcinogenicity of Carbon Black, Printing Trades and Various Substances. Monograph Programme. International Agency for Res. on Cancer, Lyon, 1995.
15. Working Group on Human Cancer Risks associated with Chrysotile Asbestos. World Health Organization (IPCS) Geneva, June 1995.
16. Secretariat on Evaluation of Chemopreventive Effect of Aspirin and Other NSAIDS for Cancer. International Agency for Res. on Cancer, Lyon, Apr. 1997.
17. Chair. Symposium on Health Risks of Water Disinfection By-products. Convened by Health Canada. Ottawa. May 1997.
18. Working Group. Meeting on Species-specificity in response to carcinogens. Monograph Programme. International Agency for Res. on Cancer, Lyon, Nov. 1997.
19. Board of Directors. Canadian Society for Epidemiology and Biostatistics. 1997-1999.
20. Working Group. Evaluation of Carcinogenicity of Various Industrial Substances. Monograph Programme. International Agency for Res. on Cancer, Lyon, Feb. 1998.
21. Canadian Coalition on Cancer Surveillance. 1997-2002.
22. External site review panel. U.S. National Cancer Institute Epidemiology Branch. June 1999.
23. Organizing Committee for Medical Research Council Workshop on Privacy of Health Data. 1999-2000.
24. Organizing Committee, EPI2001. Joint North American Congress of Canadian Society for Epidemiology and Biostatistics, Society for Epidemiologic Research, American Public Health Association (Epid) and American College of Epidemiology, Toronto, 14 – 16 June 2001. 1999-2001.
25. Coordinator of national initiative of the public health community to provide guidance on the structures and functioning of the new Canadian Institutes of Health Research. 1999-2000.
26. Organizing Committee. World Congress of the International Epidemiological Association, Montréal, 18-22 August 2002. 2001-2002.
27. President. Canadian Society for Epidemiology and Biostatistics. 2001-2003. Member of Board. 1997-1999.
28. Working Group. Evaluation of Carcinogenicity of Various Substances. Monograph Programme. International Agency for Res. on Cancer, Lyon, 2003.

29. Jury of Consensus Conference on risks and benefits of vaccination for hepatitis B. For Minister of Health of France. Organized by INSERM and ANAES. Paris 2003.
30. Public Advisory Panel. Vinyl Council of Canada. 1998-2004.
31. Advisory Panel. U.S. National Cancer Institute Brain Tumor Study. 1998-2003.
32. Scientific Advisory Committee. Boeing/UAW Workers' Health Studies. 1999-2005.
33. Institute Advisory Board. Canadian Institutes for Health Research – Institute of Circulatory and Respiratory Health. 2001-2005.
34. National Occupational Research Agenda (NORA). Joint consultative committee for US National Cancer Institute and US National Institute for Occupational Safety and Health. 2002-2005.
35. Canadian Cancer Surveillance Alliance. Consultative committee of Health Canada, Canadian Cancer Society, Provincial Cancer Registries, Statistics Canada. 2002-2003.
36. Co-president. Organizing Committee of Joint SER-CSEB Congress, Toronto 27-30 June 2005. (2004-2005).
37. Chair. Monograph Program Meeting. International Agency for Research on Cancer (WHO), France. February 2006.
38. Advisory Committee on Research Ethics and Databanks. Quebec Health Research Council (FRSQ). 2003-2011.
39. Board of Directors. American College of Epidemiology. 2003-2006.
40. Board of Directors. National Cancer Institute of Canada. 2003-2007.
41. Member Scientific Council International Agency for Research on Cancer (WHO). Lyon, France 2005-2009.
42. Elected Chair. Scientific Council International Agency for Research on Cancer (WHO). Lyon, France 2008-2009.
43. Scientific Advisory Council Canadian Partnership Against Cancer 2007-2009.
44. Working Group on Cancer Prevention, CPAC, 2007-2010.
45. Subgroup Chair and Working Group Member. Evaluation of Carcinogenicity of Non-Ionizing Radiation, Radiofrequency Electromagnetic Fields. Monograph Programme. International Agency for Research on Cancer, Lyon May 2011.
46. Member of external review panel. Helmholtz Center Munich Research Institute. Germany. July 2011.
47. Conseil Scientifique de l'Institut de Recherche en Santé Publique (IReSP). Under aegis of INSERM and Ministère de la Santé, France. 2004-2009.
48. Advisory Committee. Occupational Cancer Research Centre of Ontario. 2009-2013.
49. Member of Scientific Advisory Board of Bordeaux cancer research center SIRIC-BRIO, Bordeaux France. 2013-2018.
50. Adviser and expert witness for legal team conducting a major class action lawsuit against the Canadian tobacco industry. 2007-2016.
51. Chair of the International Scientific Council of CONSTANCES, a French national population cohort for biomedical research, the largest population cohort in Europe. 2013-2021.

OTHER SIGNIFICANT EXTERNAL CONSULTATIONS (INVITED)

1. Consultation with Quebec Ministry of Justice regarding compensation for homeowners who were advised to use formaldehyde-base home insulation - 1983.
2. Invited participant. Workshop convened by the Science Council of Canada on the future of Epidemiology in Canada, Ottawa - 1985.
3. Consultation with Government of Alberta regarding the evaluation of a report alleging significant health impact in the environment of a sour-gas plant - 1985.
4. Consultation with Quebec Ministry of Environment regarding health effects of residency near an abandoned toxic waste site in LaSalle, Quebec - 1987.
5. Invited participant. Workshop convened by Canadian Public Health Association, Environment Canada and Health and Welfare Canada on Environmental Impact Assessment, Ottawa - 1987.

6. Invited participant. Annual workshops convened by Health Protection Branch of Health and Welfare Canada to discuss the role of Canada in the SEARCH programme of the International Agency for Research on Cancer, Ottawa - 1987-1989.
7. Consultation with Quebec Cree Band Council regarding a research proposal to study developmental effects of consuming fish with high mercury levels - 1989.
8. Invited participant. Workshop convened by Ontario Industrial Disease Standards Panel on the use of epidemiologic data in workers' compensation, Toronto - December 1989.
9. Invited participant. Workshop convened by National Academy of Sciences (U.S.) on Carcinogenicity of Complex Mixtures, Tucson, Arizona - Jan 1990.
10. Invited participant. Workshop convened by Laboratory Centers for Disease Control, Health and Welfare Canada on Multiple Chemical Sensitivities, Ottawa - May 1990
11. Member of expert advisory panel to the pan-Canadian case-control study of electromagnetic fields and childhood leukemia. Sponsored by Canadian Electrical Assoc, EPRI (U.S.A.), Health and Welfare Canada. 1990-1996.
12. Organizer of Workshop to Plan a Pan-North American Case-control Study of Lung Cancer. Sponsored by Health and Welfare Canada. Toronto. March 1991.
13. Invited participant. Workshop convened by Environmental Health Directorate of Health and Welfare Canada, on Environmental Epidemiology in Canada. Ottawa. March 1992
14. Invited participant. Workshop convened by Harvard Center for Risk Analysis on implementing a new type of risk assessment. Maryland. April 1992.
15. Member of Technical Advisory Panel for epidemiology studies of foundry workers - CIIT. Research Triangle Park, N.C. Feb. 1993
16. Consultant to Health Effects Institute - Asbestos Research, on Options for Characterizing Worker Activities in Buildings, Boston. Feb. 1993.
17. Advisory panel to Laboratory Centers for Disease Control, Health and Welfare Canada, on Environmental Epidemiology under the Green Plan. March 1993.
18. Member of External Advisory Committee. Champlain Adirondack Biosphere Environmental Health Sciences Center, University of Vermont. 1993.
19. Consultant to Michigan Cancer Foundation on a variety of epidemiologic studies. 1993-1996.
20. Invited to address President Clinton's Panel on Cancer regarding priorities in cancer research. Bethesda, MD. April 1994.
21. Invited participant. Science and Technology Review Consultation. Government of Canada. Montréal. September 1994.
22. Invited participant. Strategic planning workshop to reduce Environmental Tobacco Smoking exposure. Laboratory Centre for Disease Control. Health Canada. Oct 1995.
23. Invited participant. Meeting to establish new priorities for funding. National Health Research and Development Programme of Canada. Montréal. Feb 1996.
24. Chair Scientific Advisory Committee for the Dalhousie University study of health effects of environmental and occupational pollution in the area of the Sydney, Nova Scotia steel industry. 1996.
25. Member of two Ministerial missions of the Quebec and Canadian governments to France to discuss with French experts the risks associated with low level exposure to chrysotile asbestos. Paris. Oct 1996.
26. Chair. Meeting of collaborators of European network of studies on lung cancer and smoking.
27. International Agency for Res. on Cancer, Lyon. June 1997.
28. Member of Canadian scientific delegation to United Kingdom to discuss with British experts the risk associated with low level exposure to chrysotile asbestos. London, Sept. 1997.
29. Symposium chair. Workshop to discuss methods of predicting numbers of cases of mesothelioma to be expected in various countries. Paris. Dec. 1997.
30. Invited participant and subgroup reporter. Peer Review on Hazard Assessment and Dose-Response Characterization for the Carcinogenicity of Formaldehyde by the Route of Inhalation. Health Canada and U.S. EPA. Ottawa. March 1998.

31. Co-chair. Workshop to explore the feasibility of an international collaborative study on use of cellular phones and risk of cancer. International Agency for Research on Cancer. Lyon. Feb 1999.
32. Panellist. Consensus Meeting for a Proposed Integrated National Health Surveillance Network. Health Canada. 1999.
33. Invited participant. Medical Research Council Summit Meeting on the new Canadian Institutes of Health Research. Toronto. June, 1999.
34. Invited participant. Planning group for an Institute of Population Health Research in CIHR. Jul-Dec 1999.
35. Invited speaker. Workshop for a Canadian Institute for Genetics Research. May 2000.
36. Invited participant. Workshop to explore the use of prospective cohorts to investigate gene-environment interactions in cancer etiology. National Cancer Institute. Rockville, MD. May 2000.
37. Invited participant. Founding meeting of Canadian Association for Workplace Safety and Health. Montréal. Jan 2001.
38. Invited participant. Workshop to advise Canadian Foundation for Innovation on its role in supporting population health research in Canada. Toronto, Feb 2001.
39. Invited participant. Consultative committee to advise Cancer Care Ontario on priorities in environmental cancer. April 2001.
40. Invited participant. Workshop on national priorities in cancer research. Institute for Cancer Research. CIHR. Toronto. May 2001.
41. Invited participant. Delphi process to advise Canadian Institutes of Health Research on priorities in cancer research. October-December 2001.
42. Invited participant. Delphi process to advise Cancer Care Ontario on priorities in cancer prevention. November-April 2002.
43. Session Chair. NIOSH workshop “Applying New Biotechnologies to the Study of Occupational Cancer”, Washington, D.C. May 2002.
44. Member of Advisory Panel. U.S. National Cancer Inst. Study of a Cohort of Chinese Workers Exposed to Benzene. 2002-2016.
45. Invited participant. Delphi process to advise Cancer Care Ontario on priorities in cancer prevention. November-April 2002.
46. Session Chair. NIOSH workshop “Applying New Biotechnologies to the Study of Occupational Cancer”, Washington, D.C. May 2002.
47. Organizer and Session Chair. International Epidemiological Association Meeting. Occupation and Health. Montréal. August, 2002.
48. Co-Organizer and Session Chair. Epidemiological Association Meeting. Asbestos and mesothelioma. Montréal. August, 2002.
49. Session Chair. Epidemiological Association Meeting. Environment and Health. Montréal Aug, 2002.
50. Invited participant. CIHR National Forum to devise a National Research Programme for Environmental Health. Ottawa. Sept 2002.
51. Invited participant. CIHR national forum on privacy of health data. Ottawa, November, 2002.
52. Member. Environmental and Occupational Carcinogens Advisory Group. Canadian Cancer Society. 2002 - 2004.
53. Participant. Meeting to discuss the establishment of a prospective childhood cohort in Canada. CIHR-IPPH. March 2004.
54. Member of working group on national cohort project. National Cancer Research Initiative. January-June 2004.
55. Member of advisory group on development of IDEES, Université de Montréal. January-June 2004.
56. Member, ad-hoc group to explore the feasibility of a Canadian cohort on cancer and chronic disease. 2004-2008.
57. Invited participant. Workshop to discuss the enhancement of population health research in Canada. CIHR-IPPH. June 2004.

58. Invited participant. Workshop on occupational cancer surveillance. Occupational Cancer Research & Surveillance Project (Cancer Care Ontario and the Ontario Workplace Safety & Insurance Board). February 2005.
59. Invited participant. Workshop on long-term large-scale cohorts. CIHR, December 2005.
60. Member. Advisory Scientific Committee. IBM – University of Alabama project on health of IBM manufacturing plant workers. 2006 - 2008.
61. Advisor and meeting participant. Ontario Workplace Safety and Insurance Board. Recommendations on how to develop occupational cancer research in Ontario. Toronto, 2005.
62. Invited participant. Workshop to estimate the burden of occupational cancer in the United Kingdom. UK Health and Safety Executive. Manchester. June 2006.
63. Advisory Committee to British Energy Networks Association. Workshop on the Future Needs of Electro-magnetic Fields Occupational Studies in the Electric Utility Industry. Edinburgh. September 2006.
64. Advisory Committee. IARC Monograph Programme Planning of Special Volume 100. Lyon. September 2006.
65. Grant Review Panel. IVRSP. Paris. September 2006.
66. Advisory Committee to CCRA and ICR (CIHR) on the nature of a national cohort platform. Toronto, September 2006.
67. Invited participant. Comité d'éthique de la recherche de la faculté de médecine (CERFM) : Discussion d'un projet soumis pour la création d'une banque de données et de matériaux biologiques (Research Ethics Committee of the Faculty of Medicine: Review of a submitted project to create a bank of data and biologic samples). Université de Montréal. March 2007.
68. Invited participant. Workshop to Design and Implement the Ontario Cohort Consortium Research Platform. Toronto. June 2007.
69. Invited participant. Canadian Cancer Research Agencies. Strategic Planning Consultation in Montréal. May 2009.
70. Invited participant. IARC-NORA workshop to identify gaps of knowledge on occupational carcinogens, Lyon. June 2009.
71. Consultant. State of the science workshop: evaluation of epidemiological data consistency for application in regulatory risk assessment. US EPA and Johns Hopkins School of Public Health. Baltimore. September 2010.
72. Consultant. World Health Organisation. Re-evaluation of Risk Assessments related to DDT exposure. Geneva. November 2010.
73. Invited participant. WHO workshop to develop international guidelines for control of environmental carcinogens. Asturias. March 2011.
74. Session Chair. Discovering occupational carcinogens. Congress of Epidemiology. Montréal June 2011.
75. Invited co-organiser. Symposium of Environment and Cancer. Canadian Cancer Research Conference. Toronto. November 2011.
76. Invited organiser and Chair. Symposium on Cellphones and Cancer. American Association for Cancer Research. Chicago, April 2012.
77. Member Scientific Program Committee for the 2013 Canadian Cancer Research Conference, Toronto. November 2013.
78. Member of Comité national d'épidémiologie en cancérologie. Ministère de la Santé et des Services sociaux, Quebec. 2014-2016.
79. Member, Advisory committee to Directors of Cartagene, a Quebec population cohort on genetics, environment and health. 2016-2018.
80. Member of Advisory Committee to National Cancer Institute (U.S.) study on carcinogenicity of diesel emissions. 2017-2019.
81. Member, Advisory Committee to IARC regarding the procedures and criteria of the Monograph Program of IARC on Evaluation of carcinogens. 2018.
82. Member of Advisory Committee to Minister of Health of France regarding risks associated with use of chlordecone as a pesticide in French Antilles. 2018-2021.

SIGNIFICANT INSTITUTIONAL COMMITTEES

1979-80	Member of faculty committee to negotiate a collective agreement with the Institut Armand-Frappier administration.
1982-92	Member, Research Council. Institut Armand-Frappier.
1998-2001	Member, Institutional advisory council. Institut Armand-Frappier. Institut national de la recherche scientifique
2002-2006	Excutive Committee (Comité de direction). Centre de recherche du CHUM
2002-2020	Member, Various committees of the Dept Med Soc et Preventive, including Promotions, and Recruitment.
2006-2009	Member, Various committees established to set up a new School of Public Health at l'Université de Montréal
2006-2014	Comité Scientifique de la Recherche du CHUM.

HONOURS

1. Biographee in various Who's Who in America versions. Since 1982
2. Perron-Desrosiers Prize. Granted by the Governing Council of the Institut Armand-Frappier. 1985.
3. Invited to give the annual Elizabeth Stern Memorial Lecture in U.C.L.A. School of Public Health. 1985.
4. National Health Scholar. National Health Research and Development Programme of Canada. 1988-1998.
5. Visiting Scientist Award. International Agency for Research on Cancer, Lyon. 1996-1997.
6. Prix d'excellence. Institut national de la recherche scientifique. Université du Québec. 1999.
7. Distinguished Scientist Award. Medical Research Council, Canada. 1999-2004.
8. Canada Research Chair in Environmental Epidemiology and Population Health. 2001-2015.
9. Distinguished Scientist Lecturer. US National Cancer Institute. Division of Cancer Epidemiology and Genetics. 2006.
10. Cancer Research Society–Guzzo Chair in Environment and Cancer. Since 2007.
11. Fellow Canadian Academy of Health Sciences. Since 2008.
12. Geoffrey R Howe Distinguished Contributions Award, Canadian Society for Epidemiology & Biostatistics. 2011.
13. Ranked top Canadian public health researcher in terms of research productivity by Jarvey et al. 2012.

GRANT REVIEW, JOURNAL REVIEW AND PERSONNEL REVIEW

Associate Editor

American Journal of Epidemiology (1989-1998)
International Journal of Environmental Health (1991-2016)

Contributing Editor

Journal of Public Health Policy (1982-87)
American Journal of Industrial Medicine (1996- 2016)
The Open Epidemiology Journal (2007-2012)

Chairman of grant review panels

National Health Research and Development Programme. Canada. (1990-94)
National Cancer Institute of Canada (1994-1995)

Member of grant review panels

40 times

External referee for tenure or promotion of personnel in other institutions

18 times

THESES

1. Siemiatycki J. "Space-time clustering: finding the distribution of a correlation-type statistic". M.Sc. thesis, McGill University, 1971.
2. Siemiatycki J. "Evaluation of strategies for household health surveys". Ph.D. thesis, McGill University, 1976.

ARTICLES PUBLISHED PEER REVIEW

1. Thurlbeck WM, Horowitz I, Siemiatycki J, Dunnill MS, Maisel JC, Pratt P, et al. Intra- and inter-observer variations in the assessment of emphysema. Archives of Environmental Health. 1969;18:646-59.
2. Becklake MR, Fournier-Massey G, McDonald JC, Siemiatycki J, Rossiter CE. Lung function in relation to chest radiographic changes in Quebec asbestos workers. Bulletin de Physio-Pathologie Respiratoire. 1970;6:637-59.
3. McDonald JC, McDonald AD, Gibbs GW, Siemiatycki J, Rossiter CE. Mortality in the chrysotile asbestos mines and mills of Quebec. Archives of Environmental Health. 1971;22:677-86.
4. Siemiatycki J, McDonald AD. Neural tube defects in Quebec: a search for evidence of `clustering' in time and place. British Journal of Preventive and Social Medicine. 1972;26:10-4.
5. Siemiatycki J. Mantel's space-time clustering statistic: computing higher monents and a comparison of various data transforms. Journal of Statistical Computation & Simulation. 1978;7:13-31.
6. Siemiatycki J. A comparison of mail, telephone, and home interview strategies for household health surveys. American Journal of Public Health. 1979;69(3):238-45.
7. Siemiatycki J, Brubaker G, Geser A. Space-time clustering of Burkitt's lymphoma in east Africa: analysis of recent data and a new look at old data. International Journal of Cancer. 1980;25:197-203.
8. Siemiatycki J, Richardson L. Statut socio-économique et utilisation des services de santé à Montréal. L'Actualité Economique. 1980(Avril-Juin):194-210.
9. Siemiatycki J, Richardson L, Pless IB. Equality in medical care under national health insurance in Montréal. New England Journal of Medicine. 1980;303:10-5.
10. Colle E, Siemiatycki J, West R, Belmonte MM, Crepeau MP, Poirier R, et al. Incidence of juvenile onset diabetes in Montréal - demonstration of ethnic differences and socio-economic class differences. Journal of Chronic Diseases. 1981;34(12):611-6.
11. Siemiatycki J, Day NE, Fabry J, Cooper JA. Discovering carcinogens in the occupational environment: a novel epidemiologic approach. Journal of the National Cancer Institute. 1981;66(2):217-25.
12. Siemiatycki J, Thomas DC. Biological models and statistical interactions: an example from multistage carcinogenesis. International Journal of Epidemiology. 1981;10(4):383-7.
13. Siemiatycki JA, Richardson LJ. Le défi prioritaire en santé communautaire : Élargir notre vision pour atteindre nos véritables objectifs. L'Union Médicale du Canada. 1981;110:1008-12.
14. Pampalon R, Siemiatycki J, Blanchet M. Pollution environnementale par l'amiante et santé publique au Québec [Environmental asbestos pollution and public health in Quebec]. L'Union Medicale du Canada. 1982;111(5):475-82, 87-89.
15. Siemiatycki J, Gérin M, Richardson L, Hubert J, Kemper H. Preliminary report of an exposure-based, case-control monitoring system for discovering occupational carcinogens. Teratogenesis, Carcinogenesis, and Mutagenesis. 1982;2:169-77.
16. *Baumgarten M, Siemiatycki J, Gibbs GW. Validity of work histories obtained by interview for epidemiologic purposes. American Journal of Epidemiology. 1983;118(4):583-91.
17. Hours M, Fabry J, Siemiatycki J, Francois R. Diabète insulino-dépendant juvénile. Étude descriptive dans le département du Rhône. Revue d'épidémiologie et de santé publique. 1984;32:107-12.
18. Siemiatycki J, Campbell S. Nonresponse bias and early versus all responders in mail and telephone surveys. American Journal of Epidemiology. 1984;120(2):291-301.

19. Siemiatycki J, Campbell S, Richardson L, Aubert D. Quality of response in different population groups in mail and telephone surveys. American Journal of Epidemiology. 1984;120(2):302-14.
20. *Dewar RAD, Siemiatycki J. A program for point and interval calculation of odds ratios and attributable risks from unmatched case-control data. International Journal of Bio-Medical Computing. 1985;16:183-90.
21. Gérin M, Siemiatycki J, Kemper H, Bégin D. Obtaining occupational exposure histories in epidemiologic case-control studies. Journal of Occupational Medicine. 1985;27(6):420-6.
22. Siemiatycki J. Long-term funding for epidemiologic research. Journal of Chronic Diseases. 1985;38(3):211-2.
23. Thomas DC, Siemiatycki J, Dewar R, Robins J, Goldberg M, Armstrong BG. The problem of multiple inference in studies designed to generate hypotheses. American Journal of Epidemiology. 1985;122(6):1080-95.
24. Gérin M, Siemiatycki J, Bégin D, Kemper H, Lakhani R, Nadon L, et al. Dépistage épidémiologique des facteurs cancérogènes de l'environnement de travail montréalais: un premier bilan. Travail et Santé. 1986;2(3):S42-S6.
25. *Goldberg MS, Siemiatycki J, Gérin M. Inter-rater agreement in assessing occupational exposure in a case-control study. British Journal of Industrial Medicine. 1986;43:667-76.
26. Siemiatycki J, Colle E, Aubert D, Campbell S, Belmonte MM. The distribution of type I (insulin-dependent) diabetes mellitus by age, sex, secular trend, seasonality, time clusters, and space-time clusters: evidence from Montréal, 1971-1983. American Journal of Epidemiology. 1986;124(4):545-60.
27. Siemiatycki J, Richardson L, Gérin M, Goldberg M, Dewar R, Désy M, et al. Associations between several sites of cancer and nine organic dusts: results from an hypothesis-generating case-control study in Montréal, 1979-1983. American Journal of Epidemiology. 1986;123(2):235-49.
28. Thomas DC, Goldberg M, Dewar R, Siemiatycki J. Statistical methods for relating several exposure factors to several diseases in case-heterogeneity studies. Statistics in Medicine. 1986;5:49-60.
29. *Guay D, Siemiatycki J. Historic cohort study in Montréal's fur industry. American Journal of Industrial Medicine. 1987;12:181-93.
30. Siemiatycki J, Dewar R, Nadon L, Gérin M, Richardson L, Wacholder S. Associations between several sites of cancer and twelve petroleum-derived liquids. Results from a case-referent study in Montréal. Scandinavian Journal of Work, Environment and Health. 1987;13:493-504.
31. Siemiatycki J, Wacholder S, Richardson L, Dewar R, Gérin M. Discovering carcinogens in the occupational environment: methods of data collection and analysis of a large case-referent monitoring system. Scandinavian Journal of Work, Environment and Health. 1987;13:486-92.
32. Diabetes Epidemiology Research International Group. Geographic patterns of childhood insulin-dependent diabetes mellitus. Diabetes. 1988;37:1113-9.
33. Siemiatycki J. Epidemiologic approaches to evaluation of carcinogens. In: Living in a Chemical World. Annals of the New York Academy of Sciences. 1988;534:395-9.
34. Siemiatycki J, Colle E, Campbell S, Dewar R, Aubert D, Belmonte MM. Incidence of IDDM in Montréal by ethnic group and by social class and comparisons with ethnic groups living elsewhere. Diabetes. 1988;37(8):1096-102.
35. Siemiatycki J, Gérin M, Stewart P, Nadon L, Dewar R, Richardson L. Associations between several sites of cancer and ten types of exhaust and combustion products. Results from a case-referent study in Montréal. Scandinavian Journal of Work, Environment and Health. 1988;14:79-90.
36. Siemiatycki J, Wacholder S, Dewar R, Cardis E, Greenwood C, Richardson L. Degree of confounding bias related to smoking, ethnic group, and socioecomomic status in estimates of the associations between occupation and cancer. Journal of Occupational Medicine. 1988;30(8):617-25.
37. Siemiatycki J, Wacholder S, Dewar R, Wald L, Bégin D, Richardson L, et al. Smoking and degree of occupational exposure: are internal analyses in cohort studies likely to be confounded by smoking status? American Journal of Industrial Medicine. 1988; 13:59-69.

38. Gérin M, Siemiatycki J, Nadon L, Dewar R, Krewski D. Cancer risks due to occupational exposure to formaldehyde: results of a multi-site case-control study in Montréal. International Journal of Cancer. 1989; 44: 53-58.
39. Siemiatycki J. Friendly control bias. Journal of Clinical Epidemiology. 1989;42(7):687-8.
40. Siemiatycki J, Colle E, Campbell S, Dewar RAD, Belmonte MM. Case-control study of IDDM. Diabetes Care. 1989;12(3):209-16.
41. Siemiatycki J, Dewar R, Lakhani R, Nadon L, Richardson L, Gerin M. Cancer risks associated with 10 inorganic dusts: results from a case-control study in Montréal. American Journal of Industrial Medicine. 1989;16(5):547-67.
42. Siemiatycki J, Dewar R, Richardson L. Costs and statistical power associated with five methods of collecting occupation exposure information for population-based case-control studies. American Journal of Epidemiology. 1989;130(6):1236-46.
43. Diabetes Epidemiology Research International Group. Secular trends in incidence of childhood IDDM in 10 countries. Diabetes. 1990;39:858-64.
44. Hours M, Siemiatycki J, Fabry J, Francois R. [Time clustering and temporospatial regrouping study of cases of juvenile diabetes in the district of Rhône (1960-1980)]. Revue d'épidémiologie et de santé publique. 1990;38(4):287-95.
45. Terracini B, Siemiatycki J, Richardson L. Cancer incidence and risk factors among Montréal residents of Italian origin. International Journal of Epidemiology. 1990;19(3):491-7.
46. *Dewar R, Siemiatycki J, Gérin M. Loss of statistical power associated with the use of a job-exposure matrix in occupational case-control studies. Applied Occupational & Environmental Hygiene. 1991;6:508-15.
47. Gérin M, Siemiatycki J. The occupational questionnaire in retrospective epidemiologic studies: recent approaches in community-based studies. Applied Occupational & Environmental Hygiene. 1991;6(6):495-501.
48. Payment P, Franco E, Richardson L, Siemiatycki J. Gastrointestinal health effects associated with the consumption of drinking water produced by point-of-use domestic reverse-osmosis filtration units. Applied and Environmental Microbiology. 1991;57(4):945-8.
49. Payment P, Richardson L, Siemiatycki J, Dewar R, Edwardes M, Franco E. A randomized trial to evaluate the risk of gastrointestinal disease due to consumption of drinking water meeting current microbiological standards. American Journal of Public Health. 1991;81(6):703-8.
50. Bégin D, Gérin M, de Guire L, Siemiatycki J, Adib G. Étude sur la validité des matrices emploi-exposition multisectorielles en hygiène industrielle. Revue de médecine du travail. 1992;XIX:74-9.
51. Soskolne CL, Jhangri GS, Siemiatycki J, Lakhani R, Dewar R, Burch JD, et al. Occupational exposure to sulfuric acid in southern Ontario, Canada, in association with laryngeal cancer. Scandinavian Journal of Work, Environment and Health. 1992;18(4):225-32.
52. Ursin G, Aragaki CC, Paganini-Hill A, Siemiatycki J, Thompson WD, Haile RW. Oral contraceptives and premenopausal bilateral breast cancer: a case-control study. Epidemiology. 1992;3(5):414-9.
53. Payment P, Franco E, Siemiatycki J. Absence of relationship between health effects due to tap water consumption and drinking water quality parameters. Water Science & Technology. 1993;27(3/4):137-43.
54. Siemiatycki J. Problems and priorities in epidemiologic research on human health effects related to wiring code and electric and magnetic fields. Environmental Health Perspectives. 1993;101(Suppl. 4):135-41.
55. Case BW, Dufresne A, Fraser R, Siemiatycki J, Perrault G, Takahashi K. Decoding occupational history from total lung particulate analysis: Concordance between physico-chemical analysis and occupational histories. Annals of Occupational Hygiene. 1994;38(Supplement 1):469-82.
56. Korner-Bitensky N, Wood-Dauphinee S, Siemiatycki J, Shapiro S, Becker R. Health-related information postdischarge: telephone versus face-to-face interviewing. Archives of Physical Medicine and Rehabilitation. 1994;75(12):1287-96.

57. Siemiatycki J, Dewar R, Krewski D, Desy M, Richardson L, Franco E. Are the apparent effects of cigarette smoking on lung and bladder cancers due to uncontrolled confounding by occupational exposures? Epidemiology. 1994;5(1):57-65.
58. Siemiatycki J, Dewar R, Nadon L, Gérin M. Occupational risk factors for bladder cancer: results from a case-control study in Montréal, Quebec, Canada. American Journal of Epidemiology. 1994;140(12):1061-80.
59. Takahashi K, Case BW, Dufresne A, Fraser R, Higashi T, Siemiatycki J. Relation between lung asbestos fibre burden and exposure indices based on job history. Occupational & Environmental Medicine. 1994;51(7):461-9.
60. Case BW, Dufresne A, Richardson L, Siemiatycki J, Takahashi K. Lung-retained dose following occupational exposure to silica. Applied Occupational & Environmental Hygiene. 1995;10(12):1031-6.
61. Nadon L, Siemiatycki J, Dewar R, Krewski D, Gerin M. Cancer risk due to occupational exposure to polycyclic aromatic hydrocarbons. American Journal of Industrial Medicine. 1995;28(3):303-24.
62. Siemiatycki J. Future etiologic research in occupational cancer. Environmental Health Perspectives. 1995;103 (Suppl 8):209-15.
63. Siemiatycki J, Krewski D, Franco E, Kaiserman M. Associations between cigarette smoking and each of 21 types of cancer: a multi-site case-control study. International Journal of Epidemiology. 1995;24(3):504-14.
64. Upfal M, Divine G, Siemiatycki J. Design issues in studies of radon and lung cancer: implications of the joint effect of smoking and radon. Environmental Health Perspectives. 1995;103(1):58-63.
65. Ursin G, Paganini-Hill A, Siemiatycki J, Thompson WD, Haile RW. Early adult body weight, body mass index, and premenopausal bilateral breast cancer: data from a case-control study. Breast Cancer Research and Treatment. 1995;33(1):75-82.
66. Aronson KJ, Siemiatycki J, Dewar R, Gerin M. Occupational risk factors for prostate cancer: results from a case-control study in Montréal, Quebec, Canada. American Journal of Epidemiology. 1996;143(4):363-73.
67. *Fritschi L, Siemiatycki J. Melanoma and occupation: results of a case-control study. Occupational & Environmental Medicine. 1996;53(3):168-73.
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69. *Fritschi L, Siemiatycki J, Richardson L. Self-assessed versus expert-assessed occupational exposures. American Journal of Epidemiology. 1996;144(5):521-7.
70. Haile RW, Witte JS, Ursin G, Siemiatycki J, Bertolli J, Thompson WD, et al. A case-control study of reproductive variables, alcohol, and smoking in premenopausal bilateral breast cancer. Breast Cancer Research and Treatment. 1996;37(1):49-56.
71. *Parent ME, Siemiatycki J, Renaud G. Case-control study of exposure to carbon black in the occupational setting and risk of lung cancer. American Journal of Industrial Medicine. 1996;30(3):285-92.
72. Siemiatycki J. Exposure assessment in community-based studies of occupational cancer. Occupational Hygiene. 1996;3:41-58.
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74. Payment P, Siemiatycki J, Richardson L, Renaud G, Franco E, Prévost M. A prospective epidemiological study of gastrointestinal health effects due to the consumption of drinking water. International Journal of Environmental Health Research. 1997;7:5-31.
75. Siemiatycki J, *Fritschi L, Nadon L, Gerin M. Reliability of an expert rating procedure for retrospective assessment of occupational exposures in community-based case-control studies. American Journal of Industrial Medicine. 1997;31(3):280-6.
76. Witte JS, Ursin G, Siemiatycki J, Thompson WD, Paganinihill A, Haile RW. Diet and premenopausal bilateral breast cancer - a case-control study. Breast Cancer Research and Treatment. 1997;42(3):243-51.

77. Boffetta P, Burdorf A, Goldberg M, Merler E, Siemiatycki J. Towards the coordination of European research on the carcinogenic effects of asbestos. Scandinavian Journal of Work, Environment and Health. 1998;24(4):312-7.
78. *Camus M, Siemiatycki J, Meek B. Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. New England Journal of Medicine. 1998;338(22):1565-71.
79. Gerin M, Siemiatycki J, Desy M, Krewski D. Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene, and styrene - results of a case-control study in Montréal. American Journal of Industrial Medicine. 1998;34(2):144-56.
80. Hu SW, Hertz-Picciotto I, Siemiatycki J. When to be skeptical of negative studies: pitpalls in evaluating occupational risks using population-based case-control studies. Canadian Journal of Public Health Revue Canadienne de Sante Publique. 1998;90(2):138-42.
81. *Parent ME, Siemiatycki J, Fritschi L. Occupational exposures and gastric cancer. Epidemiology. 1998;9(1):48-55.
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102. Rachet B, Siemiatycki J, Abrahamowicz M, Leffondre K. Various aspects of smoking behavior on lung cancer risk: a flexible modeling approach. National Cancer Institute, Bethesda, May 2001.
103. Siemiatycki J. Challenges to epidemiology and challenges to Canadian epidemiologists. National Student Conference of Epidemiology, Toronto, June, 2001.
104. Siemiatycki J. President's address. Congress of Epidemiology, Toronto, June, 2001.
105. Siemiatycki J. Découvrir les cancérigènes dans l'environnement: bilan des activités de recherche passées et perspectives d'avenir. Département de médecine sociale et préventive, Université de Montréal, October 2001.
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107. Rachet B, Siemiatycki J, Leffondre K, Abrahamowicz M. Relations dose-réponse entre la fumée de cigarette et le cancer pulmonaire à partir d'une étude cas-témoins à Montréal : Estimations utilisant une modélisation flexible. Congrès INRS-Institut Armand-Frappier, Sainte-Adèle, Quebec, November 2001.
108. Siemiatycki J, Camus M, Case B, Desy M, Parent, M.-É. Risque de cancer chez les résidantes des villes de l'amiante au Québec: Évaluation du risque attribuable à des « faibles » niveaux d'expositions et validation de la méthode d'évaluation de risque de l'E.P.A. Symposium sur l'amiante of Institut national de santé publique du Québec, Montréal, December 2001.
109. Laplante O, Parent M.-É, Siemiatycki J. Risque de mésothéliome et de cancer du poumon associé à l'exposition professionnelle aux fibres d'amiante, Montréal 1979-85. Symposium de l'Institut national de santé publique du Québec, Montréal, December 2001.
110. Siemiatycki J. Occupational causes of cancer: overview of the contribution of a study in Montréal, Research Day at Dept of Epidemiology and Community Medicine, University of Ottawa, April 2002.

111. Siemiatycki J. Biostatistical problems in epidemiologic case-control studies. Statistical Society of Canada, Hamilton, Ontario, May 2002.
112. Leffondre K, Abrahamowicz M, Siemiatycki J. Definition of risk sets for Cox's analysis of case-control data with time-varying exposures: A simulation study. Intended Society for Clinical Biostatistics (ISCB), Dijon, France, September 2002.
113. Siemiatycki J. Occupational causes of cancer. CCERN and Health Canada Research Workshop, Montebello, Quebec. October 2002.
114. Siemiatycki J. Occupational causes of cancer. Departmental seminar, McGill University, Montréal. November 2002.
115. Siemiatycki J. Facteurs environnementaux dans l'étiologie du cancer. Retraite annuelle du centre de recherche du CHUM, St-Sauveur, Quebec. November 2002.
116. Siemiatycki J. Environmental and occupational causes of cancer. Seminar. Cancer Care Ontario, Toronto, February 2003.
117. Siemiatycki J. The state of epidemiology in Canada. Plenary address. CSEB Student Congress, Halifax, Nova Scotia, June 2003.
118. Siemiatycki J. Occupational cancer epidemiology: the evolving big picture. Distinguished Scientist Lecture, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville MD, October 2003.
119. Siemiatycki J. Challenges in cancer epidemiology. Meeting of the Institute Advisory Board of Institute for Cancer Research, CIHR, Montréal, June 2004.
120. Siemiatycki J. Keynote address. Occupation and cancer. International Association of Cancer Registries, Beijing, September 2004.
121. Siemiatycki J. Which cancers are most important, what are the associated occupational situations and which confounders are involved? Burden of Cancer Epidemiologic Workshops, Health and Safety Executive. Manchester, UK, November 2004.
122. Siemiatycki J. Occupational causes of cancer. New Strategies for Recognizing and Preventing Occupational Disease, Canadian Center for Occupational Health and Safety, Toronto, March 2005.
123. Siemiatycki J. Occupational causes of cancer. The Respiratory Epidemiology & Clinical Research Unit, Montréal Chest Institute, Montréal, March 2005.
124. Siemiatycki J. Environnement et cancer : quels sont les risques? Les Belles Soirées public lecture series, Université de Montréal, Montréal, April 2005.
125. Siemiatycki J. An overview of environmental, occupational & lifestyle causes of lung cancer. Cancer Axis, McGill University Hospital Centre Research Institute, Montréal, June 2005.
126. Siemiatycki J. Les règles des comités d'éthique vont amputer notre capacité de prévenir des maladies et sauver des vies. Réunion de FRSQ sur les banques de données et des matières biologiques, Montréal, June 2005.
127. Siemiatycki J. Introductory comments. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
128. Siemiatycki J. The burden of occupational cancer on workers and on society. Joint Meeting of the Canadian Society for Epidemiology and Biostatistics and the Society for Epidemiologic Research, Toronto, June 2005.
129. Siemiatycki J. Revue des expositions professionnelles associées au cancer (Review of occupational exposures associated with cancer): pre-conference training session. Environnement et santé. Congrès international de l'Association des Épidémiologistes de Langue Française (ADELF), City of Québec, Quebec, September 2005.
130. Siemiatycki J. Opening session. Environnement et santé. Congrès international de l'Association des Épidémiologistes de Langue Française (ADELF), City of Québec, Quebec, September 2005.
131. Siemiatycki J. Impact de l'environnement et du milieu de travail sur le cancer : connaissances récentes. 9es Journées annuelles de santé publique (JASP), City of Québec, Quebec, November 2005.
132. Siemiatycki J. La recherche épidémiologique sur le cancer. Canadian Cancer Society - 2005 Annual Conference, City of Québec, Quebec, November 2005.

133. Siemiatycki J. Occupational EMF exposure and risk of cancer – methodological considerations. Workshop on the Future Needs of Electro-magnetic Fields Occupational Studies in the Electric Utility Industry, Edinburgh, September 2006.
134. Siemiatycki J. What is known about the modifiable causes of cancer and why we will not learn much more: Reflections on the decline of epidemiology as a tool to elucidate disease etiology. Department of Epidemiology, Biostatistics & Occupational Health, McGill University, Montréal, October 2006.
135. Siemiatycki J. Keynote Speaker. Environmental causes of cancer. 28th Annual Meeting of the International Association of Cancer Registries, Goiania, Brazil, November 2006.
136. Parent M.-E, Rousseau M.-C, Siemiatycki J, Boffetta P, Cohen A. Using the workplace as a window to study the role of diesen and gasoline engine emissions in lung cancer developpement. Invited abstract submitted to the Eleventh International Congress of Toxicology, Montréal, Quebec, July 2007.
137. Siemiatycki J. Keynote Speaker. The future of occupational epidemiology? 19th International Conference on Epidemiology in Occupational Health (EPICOH 2007), Banff, October 2007. Occup. Environ. Med. 2007 Dec; 64:46.
138. Siemiatycki J. Relationship between environmental risks and health of seniors. Workshop on Seniors' Health and the environment. Health Canada, Ottawa, February 2008.
139. Siemiatycki J. Freedom of research - is it threatening or threatened? Conference of Institutional Review Boards of Quebec, (4e Journées d'étude des CER), City of Québec, Quebec, October 2008.
140. Siemiatycki J. Cancer and Environment – Annual University of Montréal Medical Faculty Assembly, Montréal, December 2008.
141. Siemiatycki J. Impact de l'environnement et du milieu de travail sur les risques de cancer : méthodologie de recherche et résultats. Conférence en santé publique, Université Laval, May 2009.
142. Siemiatycki J. CIHR and Epidemiologic Research. CSEB, Ottawa, May 2009.
143. Siemiatycki J. Mode de vie, milieu de vie: les causes modifiables du cancer. (Lifestyles and environment: modifiable causes of cancer). Keynote address. Conference nationale pour vaincre le cancer, Montréal April 2010.
144. Siemiatycki J. Montréal case-control studies on occupation and cancer. Presentation for II International Course on occupational cancer. Instituto Nacional de Cancerologia, Bogota, Colombia, August 2010.
145. Siemiatycki J. Modifiable causes of cancer and estimates of attributable fractions. Presentation for II International Course on occupational cancer, Instituto Nacional de Cancerologia, Bogota, Colombia, August 2010.
146. Siemiatycki J. Asbestos and cancer in Quebec: a presentation of studies in three populations. Presentation for II International Course on occupational cancer. Instituto Nacional de Cancerologia, Bogota, Colombia, August 2010.
147. Siemiatycki J. An overview of recognized environmental and lifestyle causes of cancer, and their contribution to the overall burden of cancer. International Congress of Pathophysiology, Montréal, September 2010.
148. Siemiatycki J. Les causes modifiables du cancer (Lifestyles and environment: modifiable causes of cancer). Conference annuelle de la Société du cancer du Canada, division Québec, November 2010.
149. Siemiatiycki J. Alison McDonald's research on the impact of Medicare in Québec. Department of Epidemiology and Biostatistics, McGill University, Montréal, Quebec, May 2011.
150. Siemiatycki J. An overview of environmental causes of cancer. Special Symposium to honour Nobel Prize winner CRCHUM, Montréal, Quebec, June 2011.
151. Siemiatycki J. Review of IARC evaluation on cellphones and cancer. Congress of Epidemiology, Montréal, Quebec, June 2011.
152. Siemiatycki J. L'évidence concernant les risques de cancer liés à l'utilisation du téléphone cellulaire. Institut national de santé publique du Québec, October 2011.
153. Siemiatycki J. Do cellphones cause brain cancer? Canadian Cancer Research Conference, Toronto, November 2011.
154. Siemiatycki J. Do cellphones cause brain cancer? Canadian Center for Architecture. Public science lecture series, Montréal, Quebec, January 2012.

155. Siemiatycki J. Do cellphones cause brain cancer? McGill University Department of Epidemiology lecture series, Montréal, Quebec, March 2012.
156. Siemiatycki J. L'environnement et le risque de cancer. Table ronde. Conference annuelle de la Coalition Cancer, Montréal, Quebec, March 2012.
157. Siemiatycki J. An Overview of Modifiable Risk Factors for Cancer. CHUM Department of Medicine, Montréal, Quebec, March 2012.
158. Siemiatycki J. Do cell phones cause brain cancer? The epidemiologic evidence. Grand Rounds, St-Mary's Hospital, Montréal, Quebec, September 2012.
159. Siemiatycki J. The epidemiology of cell phones and brain cancer. Centre hospitalier universitaire Vaudois, Lausanne, Suisse, October 2012
160. Siemiatycki J. Occupational causes of cancer. Annual meeting of Occupational & Environmental Medical Association of Canada, Montréal, Quebec, September 2013.
161. Siemiatycki J. Fraction of lung cancer that is legally attributable to smoking: a novel parameter. ISPED, Bordeaux, France, November 2013.
162. Siemiatycki J. Some challenges in environmental cancer research. Boston University School of Public Health, Boston, Massachusetts, February 2014.
163. Siemiatycki J. Les causes modifiables du cancer: le cancer peut être évité. Symposium de La Fondation Sauve Ta Peau, Montréal, Quebec, September 2014.
164. Siemiatycki J. Using epidemiologic research to combat the tobacco industry. BIPS, Bremen, Germany, September 2015.
165. Siemiatycki J. Insights into the use of epidemiologic data in a class action lawsuit against the tobacco industry. CRCHUM division seminar, Montréal, Quebec, September 2015.
166. Siemiatycki J. Development of a methodology to estimate legally attributable fraction of lung cancer attributable to cigarette smoking. McGill Univ Dept of Epidemiology, Montréal, Quebec, October 2015.
167. Siemiatycki J. Using epidemiologic research to combat the tobacco industry. SIRIC-BRIO Cancer Centre. Bordeaux, France, November 2015.
168. Siemiatycki J. Do cell phones cause brain cancer? The epidemiologic evidence. Dept of Medicine, CHUM, Montréal, Québec, November 2015.
169. Siemiatycki J. Occupation and cancer. Conference for the 50th Anniversary of IARC, Lyon, June 2016.
170. Siemiatycki J. Contribution of epidemiology to knowledge on occupational risk factors for cancer. 34e Congrès national de Médecine et Santé au Travail, Paris, France, June 2016.
171. Siemiatycki J. The influence of JC McDonald on the evolution of epidemiology in Canada. Symposium in honour of JC McDonald. McGill Univ., Montréal, Quebec, May 2017.
172. Siemiatycki J. A survey of knowledge on occupational causes of cancer. Keynote address. International Association of Cancer Registries, Utrecht, Netherlands, October 2017.
173. Siemiatycki J. La preuve statistique au tribunal : recours collectif en situation d'incertitude. Café-statistique de la Société des statisticiens français, Paris, France, May 2018.
174. Siemiatycki J. Exposition aux gaz d'échappement diesel : quel impact sur la santé ? 35èmes journées nationales de santé au travail dans le BTP. Metz, France mai 2019.
175. Siemiatycki J. La cohorte CONSTANCE : sa place dans le monde des études de cohorte en population. Journée Constances. INSERM. Paris, France novembre 2022.

SCIENTIFIC PRESENTATIONS - OFFERED AND ACCEPTED

192 presentations between 1977 and 2022, in many different venues and on many different topics, mostly in congresses or conferences of learned societies. Mostly the presenters were my trainees or junior colleagues.

TEACHING AND TRAINING

Supervision of graduate trainees

Post-doctoral fellows – 22 completed.

PhD students - 10 completed, 2 in progress.

MSc Students – 16 completed.

Teaching – Entire Courses

"Advanced Epidemiology and Protocol Development", McGill University. 1983-85.

"Cancer Epidemiology", McGill University. 1993

"Epidemiology seminar for PhD". Université de Montréal, 2007; 2008; 2014.

"Methods of research in environmental epidemiology of cancer", Univ de Montréal, 2010; 2011; 2012; 2013.

"Intermediate Epidemiology", 3 credits. Université de Montréal, 2014; 2015.

"Protocol development for PhD", 3 credits. Université de Montréal, 2016; 2017;2018; 2019.

INVOLVEMENT IN LEGAL CASES

2008-2014	Smokers claiming cancer risks (Quebec)
2016-2019	Residents of Shannon, Quebec claiming cancer risks from Trichloroethylene
2016-2019	Women with ovarian cancer claiming damage due to use of body powders (U.S.)
2018-2021	Residents of Baie Comeau Quebec claiming cancer risks due to aluminum smelters

EXHIBIT B

EXHIBIT C
Additional Materials Considered for Jack Siemiatycki, MSc, PhD

1. IMERYS044612
2. IMERYS049952-56
3. IMERYS051371-72
4. IMERYS051442
5. IMERYS089960
6. IMERYS091279-80
7. IMERYS111220
8. IMERYS126092-97
9. IMERYS138505-11
10. IMERYS179122-23
11. IMERYS210136-37
12. IMERYS219720-22
13. IMERYS239864
14. IMERYS2419940-04
15. IMERYS242050
16. IMERYS274896
17. IMERYS284935-37
18. IMERYS288001-04
19. IMERYS288590-91
20. IMERYS303801
21. IMERYS322241-42
22. IMERYS342524-25
23. IMERYS422289-90
24. IMERYS442232-33
25. IMERYS500801
26. IMERYS-A_0001304-09
27. IMERYS-A_0011817
28. IMERYS-A_0011964-65
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30. IMERYS-A_0024367
31. IMERYS-MDL-AB_0005560-86
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37. INTERIM_JNJTALC_000001146-210
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136. JNJ000637879-81
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172. JNJTALC001911365-70
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177. LUZ001326-27
178. LUZ001441-44
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180. LUZ001873-76
181. LUZ002733-51

182. LUZ003202-03
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184. LUZ003264-67
185. LUZ004656-65
186. LUZ005090-91
187. LUZ005109-10
188. LUZ005118
189. LUZ006056
190. LUZ006507-09
191. LUZ010145-48
192. LUZ011817
193. LUZ011963
194. LUZ011964-65
195. LUZ012006-18
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197. LUZ012732-33
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203. LUZ013367-87
204. LUZ015111-12
205. LUZ015663
206. LUZ020182-86
207. LUZ021921-29
208. LUZ022044-50
209. LUZ022207-08
210. LUZ023843-35
211. MBS-CRE Production of Documents 000240-41
212. PCPC0017629
213. PCPC0052415
214. After your doctor or health care provider prescribes your ORTHO Diaphragm, 1998. (JANSSEN-000056-65)
215. Agenda: NTP Board of Scientific Counselors Report on Carcinogens (RoC) Subcommittee Meeting
216. Akhtar, Ahamed, Khan, et al. Cytotoxicity and apoptosis induction by nanoscale talc particles from two different geographical regions in human lung epithelial cells
217. Akhtar, Kumar, Murthy, et al. The primary role of iron-mediated lipid peroxidation in the differential cytotoxicity caused by two varieties of talc nanoparticles on A549 cells and lipid peroxidation inhibitory effect exerted by ascorbic acid
218. Alberg, et al. (2016) Socioeconomic status in relation to the risk of ovarian cancer in African-American women: a population-based case-control study
219. AMA Analytical Services, Inc. - Certificate of Analysis - Job Name: Task 3 - Analysis of Official Samples; Job Number: CLIN 1 - Task 3
220. American Board of Obestetrics and Gynecology, Inc. (ABOG), “Guide to

Learning in Gynecologic Oncology." Revised 4/2018.

221. American Statistical Association Statement, March 7, 2016 - "American Statistical Association releases statement on statistical significance and p-values"

222. Annie Yessian Report - Echeverria

223. Armhein, et al. (2019) Retire Statistical Significance - Supplementary Information

224. Bao Y, Bertoia ML, Lenart EB, et al. Origin, methods, and evolution of the three nurses' health studies. Am J Public Health. 2016;106(9):1573-1581. doi:10.2105/AJPH.2016.303338

225. Barnhart, K., et al. "Baseline Dimensions of the Human Vagina." Human Reproduction Vol. 21, no. 6 (2006): 1618-22.

226. Beral, et al. Collaborative Group on Hormonal Factors in Breast Cancer (2019) Type and timing of menopausal hormone therapy and breast cancer risk: Individual participant meta-analysis of the worldwide epidemiological evidence

227. Berg v. Johnson & Johnson, Final Jury Instructions

228. Berg v. Johnson & Johnson, Judgment

229. Berg v. Johnson & Johnson, Verdict Form October 4, 2013

230. Betti, M., et al. "Genetic Predisposition for Malignant Mesothelioma: A Concise Review." Mutat Res 781 (2019): 1-10.

231. Bird, Steffen, Tran and Egilman (2021) A review of the talc industry's influence on Federal Regulation and scientific standards for asbestos in talc

232. Borenstein M et al. Introduction to Meta-Analysis (2009)

233. Bureau Veritas Letter re: Johnson's Baby Powder Finished Goods Lot #22318RB (Protocol INV-106924-002) Bureau Veritas Reference: A1910246 (Preliminary Update/Results)

234. California Safe Cosmetics Act 2005

235. California State Cosmetics Program from the California Dept of Public Health - Occupational health Branch - Chemicals known or suspected to cause cancer or reproductive toxicity (P-31)

236. Campion, Alan, Kenneth J. Smith, Alexey V. Fedulov, David Gregory, Yuwei Fan and John J. Godleski. "Identification of Foreign Particles in Human Tissue using Raman Microscopy." Anal Chem (2018).

237. Cancer Prevention Coalition – May 13, 2008 Citizen's Petition to FDA seeking a cancer warning on cosmetic talc products

238. Cancer Prevention Coalition – November 17, 1994 Citizen's Petition to FDA seeking carcinogenic labelling on all cosmetic talc products

239. Carl v. J&J; Balderrama v. J&J - Defendants Johnson & Johnson, Johnson & Johnson Consumer Inc., and Imerys Talc America, Inc's joint memorandum of law in support of their motion to exclude plaintiffs' experts' general causation opinions

240. CDC. "An Introduction to Applied Epidemiology and Biostatistics. Lesson 3: Measures of Risk, Section 5: Measures of Association." Principles of Epidemiology in Public Health Practice, Third Edition.

241. Cesario, S - Powerpoint "Feminine hygiene product use and the risk of ovarian cancer"

242. Cesario, Sandra. PTT-Feminine hygiene product use and the risk of ovarian cancer (Unpublished).

243. Committee on the State of the Science in Ovarian Cancer Research; Board on Health Care Services; Institute of Medicine; National Academies of Sciences, Engineering, and

Medicine. Ovarian Cancers: Evolving Paradigms in Research and Care
244. Cormier (2011) Advancing FDA's regulatory science through weight of evidence evaluations
245. Cramer, Daniel W. and Allison F. Vitonis. “Signatures of Reproductive Events on Blood Counts and Biomarkers of Inflammation: Implications for Chronic Disease Risk.” PLoS ONE 12(2) (2017).
246. Crowley M. (November 12, 2018) Rule 26 report of Michael M. Crowley, PhD regarding the fragrance chemical constituents in Johnson & Johnson Talcum Powder Products
247. D. L. Longo, R. C. Young. Cosmetic talc and ovarian cancer (1979)
248. D. L. Longo, R. C. Young. Letter to the Editor: Cosmetic talc and ovarian cancer (1979)
249. Daniel Cramer Report - Echeverria
250. Daniel Cramer Supplemental Report - Echeverria
251. Daubert Order and Opinion, MDL No. 2738
252. David Steinberg publications list
253. David Steinberg signed verification Di Saia, P. J. (2015). Letter to Kathleen A. Frazier. Unpublished letter.
254. David Steinberg, CV
255. David Steinberg, expert report
256. David Steinberg, FRAPS Exhibit 14: Statement of Michael M. Landa, J.D.
257. Dawson, et al. (2018) Endometriosis and endometriosis-associated cancers: new insights into the molecular mechanisms of ovarian cancer development
258. Defense Expert Reports from Blaes Case: DeSesso; Hoel; Di Saia; Muscat; Hopkins
259. Deposition Exhibit of John Hopkins – 28 (November 5, 2018)
260. Deposition Exhibit of Julie Pier – 47 (September 13, 2018)
261. Deposition Transcript & Exhibits - John Hopkins, MDL No. 2738 (Aug. 16 – 17, 2018, Oct. 17, 2018, Nov. 5, 2018)
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263. Deposition Transcript & Exhibits - Julie Pier, MDL No. 2738 (September 12 – 13, 2018)
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EXHIBIT C

PRIOR DEPOSITION AND TRIAL TESTIMONY OF JACK SIEMIATYCKI, MSc, PhD

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